Cognitive and neural embodiment of artificial-arms in individuals with hand-absence

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Thesis Abstract

In the typically developed brain, numerous networks and regions are involved in sensing, actuating and understanding hand functions. In this thesis I take a neurocognitive approach to provide a better understating of how prosthesis users harness hand-specific resources to support their prosthetic limb (embodiment). In a series of cognitive, motor and neural studies, I test two distinct populations: congenital one-handers who are born without a hand and acquired amputees who lost their hand in adulthood, to investigate the processes underlying upper-limb prosthesis use.

First, available hand-related resources were assessed in each of the tested populations using a visual hand laterality task. Congenital one-handers were less efficient than amputees in processing visual hand information, possibly due to atypical available motor hand resources. This finding reaffirms the notion of 'embodied cognition' – that our motor repertoire shapes visual perception and cognition. This was further supported by a significant relationship between amputees' ability to move their phantom hand and their visual hand processing efficiency. Within the embodiment framework presented in this thesis, having different hand resources could potentially lead to different capabilities in prosthetic-limb use.

Next, using fMRI brain decoding analysis, I probed the neural representation of prostheses in relation to hands and tools, within the visual cortex. Increased levels of prosthesis use were associated with a formation of a novel neural visual 'prosthesis' category. This experience-dependent plasticity was observed in both congenital one-handers and amputees, pointing towards high levels of flexibility in occipitotemporal cortex. These findings challenge the naïve notion of neural embodiment, since prosthesis representation did not become more similar to hand representation.

Finally, the control dynamics of prosthetic-arms were assessed using several reaching and localisation tasks. Motor reaching accuracy with a prosthesis was found to depend on early life experience with a hand (either prosthetic or biological). Specifically, the ability to efficiently perform visually guided reaches with a prosthesis is impaired in the absence of early experience. These findings point towards a possible reliance of prosthesis use on neural hand-specific processes and provide evidence for a sensitive developmental period for sensorimotor control.

Taken together, this thesis provides a comprehensive overview of the multifaceted phenomenon of embodiment, shedding light on the underlying processes supporting human-machine interactions, and expanding our understanding of the development and plasticity of body representation.

This thesis contains approximately 33,500 word

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List of Acronyms

1D	1 dimensional
2D	2 dimensional
AMP	amputation
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BET	brain extraction tool
BF	Bayes factor
BOLD	blood oxygenation level dependent
cm	centimetres
Cond	condition
Cosm	cosmetic
DARPA	Defence Advanced Research Project Agency
DOF	degrees of freedom
EBA	Extrastriate Body-selective Area
etc	etcetera
F	female
FEAT	fMRI Expert Analysis Tool
FILM	FMRIB’s Improved Linear Model
FLIRT	FMRIB’s Linear Image Registration Tool

fMRI	functional magnetic resonance imaging
FNIRT	FMRIB’s Nonlinear Image Registration Tool
FSL	FMRIB Software Library
FWHM	full-width half-maximum
GLM	general linear model
hIP	human intraparietal
HRF	haemodynamic response function
Hz	hertz
IPS	Intra Parietal Sulcus
L	left
LDC	linear discriminant contrast
M	Male
MAL	Motor Activity Log
MCFLIRT	motion correction using FMRIB’s Linear Image Registration Tool
Mech	mechanical
mm	millimetres
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
ms	milliseconds
Myo	myoelectric

NA	not available
NHS	United Kingdom National Health Service
OSF	Open Science Framework
OTC	Occipitotemporal cortex
PAL	Prosthesis Activity Log
Pros	prosthesis
R	right
rmANCOVA	repeated measures ANCOVA
ROI	region of interest
RSA	Representational similarity analysis
RT	reaction time
s	seconds
s.e.m	standard error of the mean
SD	standard deviation
TE	echo delay time
TH	trans-humeral
TR	trans-radial
TR	repetition time
Y	years

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Introduction

0.1 Upper-limb Prosthetics

0.1.1 Prosthesis use following hand loss

A loss of a hand can have a devastating impact on the quality of life and employment of individuals, who are otherwise young and healthy (Østlie et al., 2011). Contrary to the general public belief, individuals missing a hand (either through congenital or acquired circumstances, hereafter, one-handers) are not always keen to use a prosthetic device. Reports show that only 45-56% of one-handers use a prosthesis regularly (Jang et al., 2011; Raichle et al., 2008), and that 70% of amputees are dissatisfied with their prosthesis (Jang et al., 2011). Moreover, the vast majority of users report they only wear the prosthesis for cosmetic reasons (Datta et al., 2004).

Prothesis use and abandonment are complex phenomena and are influenced by the person's physical (e.g., below-elbow vs above-elbow limb loss, origin of limb loss), mental (e.g., coping with trauma) and social (e.g., lifestyle) conditions (Biddiss & Chau, 2007b; Kerver et al., 2020). Other factors involve the quality of healthcare and rehabilitation, for example, individuals fitted with a prosthesis before the age of two (following congenital limb-loss) or six months after amputation were 16 times more likely to continue prosthesis use (Biddiss & Chau, 2008). When one-handers are asked directly, causes for prosthesis rejections include awkward control over the device, lack of tactile feedback, and complex training requirements (Engdahl et al., 2015; Jang et al., 2011; Østlie et al., 2012). However, it is not clear whether low usage is a consequence of poor technology, or if there are other inherent cognitive limitations that come in the way of prosthesis adoption.

0.1.2 Upper-limb prosthetics and robotic hand technology

In recent years there has been an exponential increase in the amount of resources dedicated to the development of robotic hands. The number of robotic hands developed in the last decade has almost tripled compared to the previous one (Piazza et al., 2019; See Figure 0.1A). As the hand has important motor, sensory and social functions, creating a robotic equivalent to the human hand remains one of the biggest challenges in robotics. Until recent years, robotic hand designs strived to mimic the hand in shape and complexity (Vujaklija et al., 2016), however that approach resulted in overly complex and impractical designs. Current trends focus on hand simplification in both design and control and move away from biomimicry (Makin et al., 2020; Piazza et al., 2019).

In practice, most one-handers do not use robotic prostheses but instead wear cosmetic and mechanical prosthetic devices (see Figure 0.1B), with underlying technology that is at least a century old (Østlie et al., 2012). Furthermore, no real advantage was found for robotic (myoelectric) prostheses over mechanical ones (Carey et al., 2017). For example, one of the most ambitious and generously-funded hand prosthesis projects, the DEKA Arm[1] (Resnik et al., 2014), has yet to show tangible functional improvements over conventional prostheses (Bloomer & Kontson, 2020; Cowley et al., 2017). It appears that the functionality of the prosthesis depends on how it is customised by the user, rather than the developer. For example, some individuals may use a motorised prosthesis in a cosmetic way, rarely utilising its capabilities, while others will use a cosmetic device to perform elaborate tasks. Therefore, I propose that more resources should be invested not only in developing the technology of prosthetic hands but also in providing a deeper understanding of the interface between the prosthesis and the user, both body and brain. Creating a reciprocal discussion between the fields

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[1] Developed under the Revolutionizing Prosthetics Program through DARPA funding

of engineering, rehabilitation and cognitive neuroscience could generate new solutions to these old problems, thus pushing this field forward.

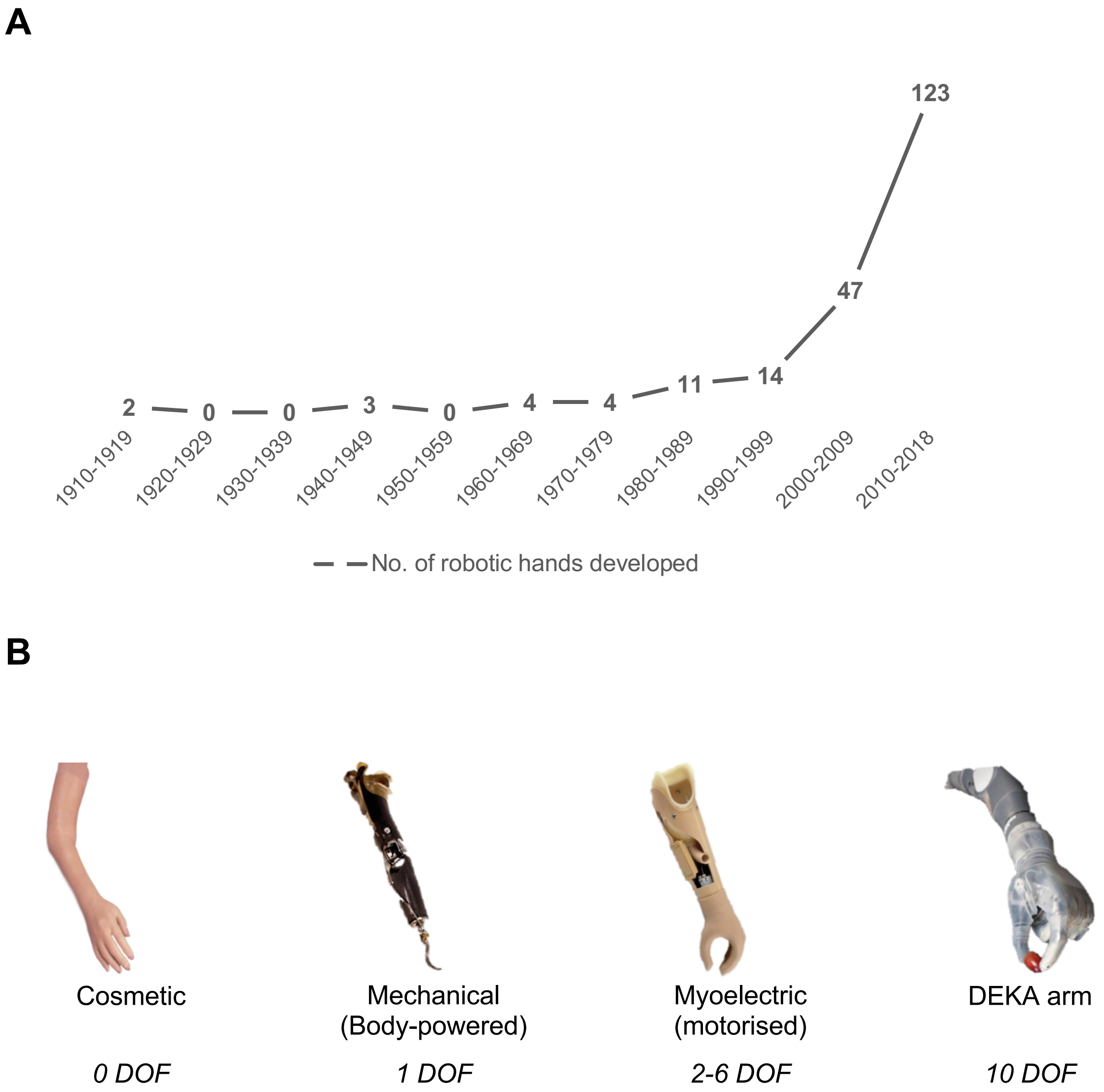

Figure 0.1. *Prosthetic-limb development and device types.* (A) Number of robotic hands developed by decade. Plotted from data published in Piazza et al. 2019 (B) Different types of prostheses and their built-in degrees of freedom (DOF).

0.2 Prosthesis embodiment

Embodiment is an umbrella term for the multi-sensory association of external objects with body representation, in other words, it is the ability to relate to an external object as if it was a part of our body (de Vignemont, 2011). Perhaps the most likely candidate to achieve embodiment are body-part substitution devices, such as prostheses (Makin et al., 2017). A popular (and yet rarely tested) assumption is that embodying the prosthetic arm as a hand, can improve prosthesis usage (Beckerle et al., 2018; Giummarra et al., 2008; Hellman et al., 2015a; Longo et al., 2016; Marasco et al., 2018; Pazzaglia & Molinari, 2016; Rognini et al., 2019; Tyler, 2015). This rationale is a key component in the biomimicry approach to prosthetic arm design discussed earlier. However, there is currently little empirical evidence to show that embodiment actually relates to everyday behaviour with artificial limbs, let alone that embodiment benefits users (Bekrater-Bodmann, 2020; Although see Appendix C).

In order to study embodiment, we must first agree on its empirical definition. Previous efforts to test and induce prosthesis embodiment have been centred on the rubber hand illusion (an illusion of body ownership over a prosthesis) showed mixed success (D'Alonzo et al., 2015; Ehrsson et al., 2008; Marasco et al., 2011; Mulvey et al., 2012; Rognini et al., 2019). Embodiment is a compound phenomenon, therefore the study of embodiment can take different forms: *phenomenological* – does the prosthesis feel like my hand?; *cognitive* – do I react with the prosthesis like I would with my own hand?; *neural* – is the prosthesis represented in the brain via the same mechanisms as a hand (de Vignemont, 2011, 2017; Makin et al., 2017). Past studies, including those cited above, have mostly focused on the *phenomenological* level (e.g., Murray, 2008). In a pioneering study, Van Den Heiligenberg and colleagues tested *neural embodiment* by measuring neural activity levels in hand-selective visual areas when viewing images of prostheses. They found that individuals who used their prosthesis more in daily lives also showed stronger activity in these hand-selective areas while viewing prosthetic limb images (Van Den Heiligenberg et al., 2018). While an important finding, on it's own it still does not provide proof of prosthesis *neural embodiment.* This is because activity in this brain area, even if pre-selected for its preference for hand images, may reflect sensitivity to features that are not exclusive to hands. The prostheses being represented as a hand is only one of several possible interpretation of this fascinating result which is discussed further in Chapter 2. Thus there are big theorhetical and empirical gaps in the study of prosthesis embodiment, with the *neural* and *cognitive* levels rarely studied, let alone the relationships between the different levels.

0.3 Hand representation in individuals missing a hand

In the typically developed brain, numerous networks and regions are involved in sensing, actuating and understanding hand functions (Brozzoli et al., 2011; Ejaz et al., 2015; Hardwick et al., 2018; Orlov et al., 2014). Ideally, prosthesis users could harness this already established infrastructure to represent and control their prosthetic-limb (*neural embodiment*). However, besides the physical disability, the loss of a hand also means the loss of organised input from the limb to the nervous system. Input loss can have a significant effect on the nervous system (de Heering et al., 2016; Walton et al., 1992), possibly resulting in neural changes to arm and hand representation in the brain. Therefore, to be able to answer the question of whether one-handers can utilise the biological hand's neural resources we must first determine what happens to these resources when the hand is no longer there.

The organisation (or reorganisation) of the nervous system will highly depend on the cause of hand absence. The two main causes for hand absence are: (1) a deviation in foetal development that result in the hand never developing[2]; (2) A planned or accidental amputation of a fully developed hand. Individuals born without a hand will be hereafter referred to as congenital one-

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[2] While there are some variations in the reasons for congenital hand absence (Oberg, 2018), for the purpose of this thesis we will group all individuals born without a hand as congenital one-handers.

handers (or congenitals in short) and individuals who lost their hand in adulthood will be hereafter referred to as acquired amputees (or amputees in short).

0.3.1 Acquired amputees: Phantom hands and persistent representation

As mentioned above, following amputation, the fully developed upper-limb neural representation of acquired amputees is subjected to a dramatic loss of organised input from the missing limb. Surprisingly, despite the absence of a hand, the majority of acquired amputees report experiencing sensations arising from their missing limb (i.e., phantom sensations, ranging from tingling to extremely painful; Makin & London Plasticity Lab, 2020). In search for the neural origins of the phantom limb phenomenon and specifically phantom limb pain, researchers discovered that following amputation the representation of neighbouring body parts, and specifically the lips, "invade" the territory that was previously occupied by the missing hand (Flor et al., 1995, 2006). However, this observed neural reorganisation, often referred to as the "maladaptive plasticity model", has been critically challenged (Jutzeler et al., 2015; Mezue & Makin, 2017). Rather than maladaptive reorganisation in the primary sensory hand area, there has been accumulating evidence showing the missing hand representation of amputees remains persistent following amputation (Bruurmijn et al., 2017; Kikkert et al., 2016, 2018; Makin, Scholz, et al., 2013; Wesselink et al., 2019). Brain activity recorded during phantom hand movements was shown to be similar to that of controls moving their hands in both magnitude (Kikkert et al., 2018; Makin, Scholz, et al., 2013) and representational structure (Kikkert et al., 2016; Wesselink et al., 2019). Moreover, cortical stimulation of amputee's missing hand primary motor area elicits the sensation of phantom movements (Bestmann et al., 2006; Cohen et al., 1991; Hess et al., 1986; Reilly & Sirigu, 2008). In summary, while some reorganisation does take place following amputation, it seems to be limited (Makin et al., 2015;

Raffin et al., 2016) and more importantly for the purposes of this thesis, the hand representation remains generally preserved.

0.3.2 Congenital one-handers: Atypical development and adaptive plasticity

Congenital one-handers, unlike acquired amputees, have never had experience with a biological hand on their missing side. Growing up without a complete arm means they had an atypical developmental trajectory both in terms of the inputs to their upper-limb neural resources and in terms of the motor strategies they adopted to compensate for their limb absence. Current views consider neural development an interaction between predetermined maturation based on a genetic template and experience, or as it is more commonly known: nature vs. nurture (Adolph & Franchak, 2017; Karmiloff-Smith, 1998; Krubitzer & Prescott, 2018). In the context of hand representation in congenital one-handers it is unclear which of these two forces will determine the fate of the neural resources and representations of hands across the brain.

Studies in both congenital one-handers and individuals born with no hands (bilateral congenital hand absence) have found that the deprived primary sensorimotor hand area becomes activated during movement of other body-parts such as feet, mouth, abdomen and residual-limb (Hahamy et al., 2017; Stoeckel et al., 2009a; Striem-Amit et al., 2018a). Since congenital one-handers use these body-parts to compensate for their limb-absence, this neural reorganisation has been speculated to be the consequence of experience, i.e., adaptive plasticity (Makin & London Plasticity Lab, 2020). Providing further evidence of adaptive plasticity, inter-hemispheric functional connectivity between the two sensorimotor hand areas of congenital one-handers were shown to be related to individuals' everyday behaviour, i.e. individuals who use their residual-limb more show higher (control-like) levels of connectivity between the hemispheres (Hahamy et al., 2015).

In addition to experience, the neural topographical organisation of sensory cortex is also known to be in part determined by genetics (Miyashita-Lin et al., 1999; Rubenstein et al., 1999). It could be argued then that regardless of the undisputed role of experience in shaping brain organisation and function, the canonical brain infrastructure may still exist. Presently, there is no strong evidence to support this idea. Unlike amputees and controls, the canonical hand structure in sensorimotor cortex was not observed in congenital one-handers (Wesselink et al., 2019). Moreover, cortical stimulation of one-handers missing hand primary motor area did not elicits phantom sensations, but instead evoked contractions in residual-limb and even facial muscles (Amoruso et al., 2021; Reilly & Sirigu, 2011). A small minority of congenital one-handers report experiencing phantom limb sensations (Brugger, 2012). However, the mechanism behind this phenomenon remains unclear. Theories range between foetal limb-movements, inter-hemispheric transfer from the intact hand, and action observation of others (Brugger, 2012; Reilly & Sirigu, 2011; Walsh et al., 2015). There is however a general agreement that these do not arise from primary sensorimotor representations and might originate from either premotor or visuomotor representations. To conclude, congenital one-handers seem to lack a neural sensorimotor hand-representation for their missing hand and this “vacant” neural real-estate has possibly been repurposed to control other body-parts.

0.3.3 Beyond sensorimotor representation

While the previous two sections focused on the primary sensorimotor hand areas in the brain, as stated – resources devoted to hands and hand-actions span far beyond the sensorimotor cortex. In particular, visual information of our hands and the objects in our close proximity have a crucial role in guiding hand-actions (Honda et al., 2012; Körding & Wolpert, 2004a; Saunders, 2004). Unlike sensorimotor cortex, the visual hand representation of individuals born with no hands was found to be not significantly different from controls (Striem-Amit et al., 2017).

Behavioural studies in individuals born with no hands show that visual body perception in these individuals is also unaffected by their lack of motor hand experience (Vannuscorps et al., 2012; Vannuscorps & Caramazza, 2015, 2016). Based on these results, the authors argue that visual hand representation is either innate or that the experience of observing the hands of others is sufficient to generate a typical visual hand representation. However, as these are null effects that rely on a very small sample (*n*=1-5), more evidence is needed to make any strong conclusions. Contrarily, congenital one-handers were shown to differ from controls in their semantic representation of hands (van den Heiligenberg et al., 2017). More specifically, congenital one-handers showed greater conceptual similarity between the tools and hands. Furthermore, the semantic representation of hands in amputees has been shown to be affected by age at hand loss, i.e., the more years one had to accumulate hand experience the more ‘typical’ their hand-tool semantic representation is.

The studies reviewed above directly investigate hand representation. The space immediately surrounding us is known to be represented relative to our hands (peri-hand space; Graziano et al., 1997; Makin et al., 2012). Therefore, hand-absence could potentially impact visuospatial processing of other objects in our vicinity. Indeed, behavioural research on peri-hand space has found that both congenitals and amputees show a mild visuospatial bias against their missing hand side (Makin et al., 2010)(Makin, Wilf, Schwartz, & Zohary, 2010). To summarise, some aspects of visual hand representation appear to be stable, while visuospatial and semantic aspects of hand representation might be more sensitive to experience.

0.4 Aims of this thesis

In this thesis I take a neurocognitive approach to provide a better understating of how prosthesis users relate to their prosthesis on the neural and cognitive levels. Inspired by the popular notion of embodiment I focus on the overarching question: **can one-handed individuals harness**

hand-specific resources to support their prosthetic-limb? Comparing congenital one-handers and acquired amputees throughout the thesis allows me to expand this question further and investigate the plasticity drivers and limitations of different cognitive and neural processes underlying upper-limb prosthesis use.

As mentioned in the previous sections, assessing which hand-related resources are available to each of our tested one-handed populations is an important prerequisite for the study of prosthesis embodiment. In Chapter 1, the missing-hand representation was evaluated using a visual hand laterality judgement task that is known to rely on motor knowledge. Contrary to previous finding in individuals with no hands (Striem-Amit et al., 2017; Vannuscorps et al., 2012; Vannuscorps & Caramazza, 2016), I show that the visual processing of hands *is* affected by motor experience, with congenital one-handers being less effective at judging hand laterality compared to amputees and controls. I propose that this is due to their limited motor experience, based on this interpretation, I make use of a computational simulation to replicate the empirical results. Amputees' ability to move their phantom hand predicts their visual hand laterality task performance, providing further strong evidence that people utilise whatever available motor resources they have when making bodily judgments.

In Chapter 2, using fMRI brain decoding analysis, I probe the information content underlying prosthesis visual representation by analysing individual's activity patterns as they view images of prostheses, hands and tools. This allows us to directly test *neural embodiment*, that is, to what extent prostheses are represented as a hand versus a tool. A naïve embodiment prediction would be that if prosthetic-limbs and hands share neural resources, their neural activation pattern (representation) would become more similar with increased use of the prosthetic-limb. Surprisingly, in prosthesis users, prostheses representations are more isolated from their natural 'hand' and 'tool' visual categories and the more a user relies on their prosthesis in daily life the more isolated that representation is. Therefore, despite benefiting from hand-selective cortical resources (Van Den Heiligenberg et al., 2018), the prosthesis is not necessarily ‘embodied’.

Finally, in Chapter 3**,** testing *cognitive embodiment*, I assessed whether the control dynamics of a prosthetic-limb are similar to those of a hand. I found that congenital one-handers show motor deficits when controlling an artificial arm, in comparison to acquired amputees. I further show that the earlier a congenital started using an artificial arm (e.g., infants vs. toddlers), the milder their motor deficit is, meaning there is a narrowing developmental period for successful artificial-arm integration. This study challenges current popular views on sensorimotor plasticity and points to important limitations of motor learning in adulthood set by early-life experience.

Together, these studies are designed to provide a more comprehensive understanding of how the brain can best support prosthesis use, with opportunities to inform prosthesis design and rehabilitation in the future. While this project is motivated by a clinical need it also informs basic neuroscience and deepens our understanding of the plasticity of body representation.

Chapter 1 | Visuomotor hand representation in individuals missing a hand as assessed by the hand laterality judgment task

Adapted from:

Maimon-Mor, R. O., Schone, H. R[3]., Moran, R., Brugger, P., & Makin, T. R. (2020). Motor control drives visual bodily judgements. *Cognition*, *196*, 104120.

Chapter Abstract

The 'embodied cognition' framework proposes that our motor repertoire shapes visual perception and cognition. But recent studies showing normal visual body representation in individuals born without hands challenges the contribution of motor control on vision. Here, we studied hand laterality judgements in three groups with fundamentally different visual and motor hand experiences: two-handed controls, one-handers born without a hand (congenital one-handers) and one-handers with an acquired amputation (amputees). Congenital one-handers, lacking both motor and first-person visual information of their missing hand, diverged in their performance from the other groups, exhibiting more errors for their intact hand and slower overall reaction-times. Amputees, who have lingering non-visual motor control of their missing (phantom) hand, performed the task similarly to controls. Amputees' reaction-times for visual laterality judgements correlated positively with their phantom-hand's motor control, such that deteriorated motor control associated with slower visual laterality judgements. Finally, we have implemented a computational simulation to describe how a mechanism that utilises a single hand representation in congenital one-handers as opposed to two in controls, could

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[3] Hunter R. Schone carried out some of the work on this study under my supervision

replicate our empirical results. Together, our findings demonstrate that motor control is a driver in making visual bodily judgments.

1.1 Introduction

Converging evidence suggests that our sensorimotor body experiences affect the way visual information is interpreted (Hagura et al., 2017; Makin et al., 2010; van den Heiligenberg et al., 2017) and even processed (Aglioti et al., 2008; Maimon-Mor et al., 2017). According to this view, also known as 'embodied cognition' (Wilson, 2002), our bodily interactions with the environment, and motor control in particular, may play a fundamental role in the development of our perceptual and cognitive abilities. If the theory of embodied cognition is verified, any attempt to accurately describe perception and cognition (e.g., developing artificial models of these processes), should consider visuomotor processing as a bidirectional process.

The most compelling evidence for the role of motor control in driving visual processing comes from visual body representation, and hand representation in particular. Visual hand laterality judgment tasks have been previously used to exemplify the contribution of prior motor experience on visual body representation, with response profiles reflecting the biomechanical properties of hand postures, i.e. longer reaction times for more physically awkward (but not visually complex) postures (Cooper & Shepard, 1975; Parsons, 1987, 1994). However, while theoretically appealing, the notion that motor experience is fundamental for visual body perception has been recently challenged by studies performed in one to five individuals with congenital absence of both hands (Vannuscorps et al., 2012; Vannuscorps & Caramazza, 2015, 2016). Despite not having any motor hand experience, visual hand perception (Vannuscorps & Caramazza, 2016), representation (Striem-Amit et al., 2017) or judgements (Vannuscorps et al., 2012) were reported to not differ from those of typically developed two-handed controls. As stated in the introduction, it has been suggested that the ability to process visual body information is either innate or depends on passive (3rd person) visual experience accumulated by observing others and is therefore entirely decoupled from motor experience.

While passive visual experience alone might be sufficient to capture the approximate biomechanical constraints of a human hand, when judging more complex postures involving atypical finger and wrist orientations, individuals may increase their reliance on their motor control. To determine whether motor or visual experience is integral in more challenging decision making, we tested laterality judgements of images of hand postures with varying degrees of biomechanical complexity (Moseley, 2004) in three groups of individuals, with similar passive visual experience, but different amounts of active (1st person) visual and motor control (both past and present; see Table 1.1): (i) two-handed *controls* (*n*=21), (ii) *congenital one-handers* (*n*=17), and (iii) acquired amputees with varying degrees of phantom motor abilities (*n*=16; see Table 1.2 for demographic and clinical details). Participants were asked to verbally indicate whether the observed laterality of a given hand posture is left or right (See Figure 1.1A for sample stimuli and Supplementary Figure S1 for the complete stimuli set and classification).

If passive viewing is sufficient to construct visual body representation, all groups should perform the task equally well. If active visual and/or motor experience is essential for complete and efficient hand representation, we expect congenitals to show impaired performance in the task relative to the other groups. Never having any experience with their missing (secondary) hand, they will be limited to the motor resources of their intact hand.

Amputees, who previously had a complete representation for their now missing hand, will allow us to further test whether bodily judgments rely on past visuomotor experience or current motor control. Crucially, amputees report experiencing varying degrees of phantom sensations, and in particular individuals vary in their sense of motor control over their phantom hand (i.e. sense of kinaesthesia when asked to move their phantom hand and fingers (Kikkert et al., 2017;

Raffin, Mattout, et al., 2012; Reilly et al., 2006). Relevant to our purposes, this ongoing motor experience of the missing hand is decoupled from any relevant visual input of a hand. Therefore, we predict that if visual body judgments benefit from ongoing motor control, amputees will utilise the motor resources of their phantom hand to complete the visual laterality task.

Secondary Hand Exp. Group	Passive Visual Experience	Active Visual Experience	Motor Control
Controls (n=21) [Two-handers]	✓	✓	✓
Congenital (n=17) One-handers	✓	✗	✗
Amputees (n=16) [One-handers]	✓	Past: ✓	Past: ✓
		Phantom: ✗	Phantom: ✓✗

Table 1.1. *Summary of the visual and motor experiences across groups.* Group similarities/differences in passive/other (3rd person) visual experience, active/self (1st person) visual experience and motor control of their secondary hand (missing/nondominant in one/two handers respectively). While all groups have similar passive visual experience for seeing the hand of others, one-handers' active (self) visual and motor experience of the missing hand differ from controls. Amputees, experiencing phantom sensations, also differ in current motor experience from congenital one-handers (indicated by a crossed check mark as individuals vary in the amount of phantom motor control).

1.2 Methods

Data presented in this manuscript was collected as part of a larger study, as detailed in the Open Science Framework (https://osf.io/kd2yh/). Presently, we focus on the following tasks: hand laterality judgement and motor finger tapping (described below). All the data included in the study is available online under the OSF listing of the study (https://osf.io/b4qks/).

1.2.1 Participants

Sixteen acquired amputees (mean age ± s.e.m. = 44.8 ± 3, 4 with absent right-arm, 3 females), seventeen congenital one-handers (mean age ± s.e.m. = 41.1 ± 3, 4 with absent right-arm, 10 females) and twenty-two able-bodied controls (mean age ± s.e.m. = 40.6 ± 3, 7 left-hand dominant; 11 females) were included in the study (see Table 1.2 for demographic and clinical details). These participants also took part in our previous reported studies (Hahamy et al., 2017; Kikkert et al., 2018; van den Heiligenberg et al., 2017; Van Den Heiligenberg et al., 2018). One control participant was excluded due to a high (27%) number of trials without responses in the hand laterality task (range of no-response trials for other participants was 0%-10.4%). Additionally, a secondary group of 13 able-bodied controls was used to establish a measure of image difficulty (see Supplementary Methods and Figure S1). Ethical approval was granted by Oxford University's Medical Sciences inter-divisional research ethics committee (Ref: MSD-IDREC-C2-2014-003) and the NHS National Research Ethics Service (Ref: 10/H0707/29). Written informed consent was obtained from all participants prior to participating in the study in accordance with ethical standards established by the Declaration of Helsinki (1964).

Subject	Gender	Age	Cause of limb loss	Age at Amp.	Level of Amputation	Missing hand side	Phantom motor control
Amp01	F	50	Tumour	45	Above elbow	Left*	18.06
Amp02	M	57	Trauma	20	Below elbow	Left*	22.06
Amp03	M	59	Trauma	40	Above elbow	Left*	21.19
Amp04	M	58	Trauma	27	Above elbow	Left	19.02
Amp05	M	53	Trauma	28	Below elbow	Left	9.14
Amp06	M	41	Trauma	27	Above elbow	Right	19.07
Amp07	M	48	Trauma	17	Above elbow	Left	13.12
Amp08	M	37	Trauma	27	Above elbow	Left	30.23
Amp09	F	46	Trauma	38	Below elbow	Left	64.08
Amp10	M	64	Trauma	33	Below elbow	Right*	20.14
Amp11	F	24	Trauma	18	Below elbow	Right	19.02
Amp12	M	49	Trauma	37	Above elbow	Left	NA
Amp13	M	29	Trauma	24	At shoulder	Left	23.01
Amp14	M	25	Trauma	18	At wrist	Left	10.04
Amp15	M	45	Trauma	20	Below elbow	Right	24.15
Amp16	M	32	Trauma	31	Above elbow	Left	230.11
Cong01	F	49	Congenital	0	Below elbow	Left	—
Cong02	F	52	Congenital	0	Below elbow	Right	—
Cong03	M	52	Congenital	0	At wrist	Left	—
Cong04	F	25	Congenital	0	At wrist	Right	—
Cong05	M	49	Congenital	0	Above elbow	Left	—
Cong06	F	28	Congenital	0	At wrist	Left	—
Cong07	M	38	Congenital	0	Below elbow	Left	—
Cong08	F	27	Congenital	0	Below elbow	Left	—
Cong09	M	60	Congenital	0	At wrist	Left	—
Cong10	F	34	Congenital	0	Below elbow	Right	—
Cong11	F	36	Congenital	0	Below elbow	Right	—
Cong12	F	41	Congenital	0	Below elbow	Left	—
Cong13	F	61	Congenital	0	At wrist	Left	—
Cong14	M	25	Congenital	0	Below elbow	Left	—
Cong15	M	34	Congenital	0	At wrist	Left	—
Cong16	M	38	Congenital	0	Below elbow	Left	—
Cong17	F	49	Congenital	0	At wrist	Left	—

Table 1.2. *Demographic and clinical details of acquired amputees and congenitals one-handers.* M/F = Male/Female; NA = not available. Age at Amp. = Age at amputation; For 'Missing hand side', asterisk

(*) = amputees that had their dominant hand amputated. Phantom motor control is measured as the average time in seconds it took participants to complete a full phantom finger-thumb opposition cycle.

1.2.2 Hand Laterality Judgement Task

1.2.2.1 Experimental Procedure

All participants responded to a set of hand stimuli which included 24 unique egocentric photographs of right hands, in postures that ranged from biomechanically simple to awkward (obtained from *L. Moseley)*. These images were digitally mirrored to construct 24, otherwise identical, photographs of left hands (see example images in Figure 1.1A). Participants completed two experimental blocks; each included the 48 total hand images. Hand images were presented in a random order using Presentation software (version 16.4). Participants were seated comfortably in front of a laptop computer while wearing a lapel microphone on their collar. Participants were instructed to rest their hand/s in their lap and were specifically instructed to not attempt to make any volitional movements, throughout the task. Participants responded vocally by indicating the hand laterality (left or right) of each presented image as fast as possible, while maintaining high accuracy. Each experimental trial consisted of the presentation of a hand image for a maximum of 5 seconds (see Figure 1.1B), preceded by a 1 second fixation cross. Time from the start of the image display to voice onset was recorded as the participants' reaction time (RT). The experimenter recorded the subject's response (i.e., 'right' or 'left') via a keyboard press, which terminated the trial.

1.2.2.2 Data Analysis

All audio recordings and the appropriate classification of reaction-times were verified offline by a naive experimenter. Trials with noisy recordings (mean of 2.8% of trials per participant) were excluded from further analysis. Accuracy was computed as the proportion of correct response of all valid trials. Only trials with correct responses were included in the RT analysis.

To compare between the one-handed groups and controls, the missing hand was matched to the non-dominant hand of controls, and the intact hand was matched to the dominant hand of controls. For simplicity, hereafter, we will refer to the dominant hand of controls as intact, and the nondominant hand as missing.

RTs were logarithmically transformed in order to correct for the skewed RT distribution and satisfy the conditions for parametric statistical testing. Transformed RTs deviating more than 3 standard deviations from the participants' means (separately for each condition) were removed. No more than 2 trials per participant were removed and the number of excluded trials did not differ between groups. The transformed RTs were analysed in a repeated-measures analysis of covariance (rmANCOVA; after testing for normality using the Shapiro Wilks test, $p>0.05$), with a between-subject factor of group (controls/amputees/congenitals), within-subject factors of difficulty (easy/hard) and hand (intact/missing). To reduce error variance due to the large age range of our participants (25-60) and to increase statistical power (Fozard et al., 1994), age was included as an a priori covariate. There were no significant interactions with age, thereby affirming homogeneity of regression slopes (as detailed in Supplementary Tables S2-S3). The measure of image difficulty was established by using data from a secondary control group (see Supplementary Methods), splitting the images to easy and hard based on the median RT of all images. Accuracy analysis was carried out using a rmANCOVA with the same conditions and covariates as described above. For both RT and accuracy data, outlier participants were identified as deviating by more than 3 standard deviations from their group mean, for each condition/group separately. Subsequently, a single outlier case was identified. ANOVA tests were repeated with the outlier excluded and reported no differences in our results.

Post-hoc comparisons of interactions were performed using paired t-tests within group when applicable or separate ANCOVA's across groups with age as a covariate for each level of the within-group variable. Post-hoc comparisons of group effects were performed using an ANCOVA with age as a covariate for each pair of groups.

To examine biases in responses, leading to divergent profiles of errors across hands, Signal Detection Theory (Green & Swets, 1966; Stanislaw & Todorov, 1999) was used. This approach can separate a change in bias from changes in discriminability between the two hands (calculated using Lindeløv, 2011). We set up "signal" as the probability space of seeing the intact hand, therefore a positive bias value indicates a tendency to over-report "missing hand", even when an intact hand is shown. Group differences were explored using a one-way ANOVA, with unpaired t-tests for follow-up.

1.2.3 Motor Task

To assess amputees' phantom hand motor control, a finger-thumb opposition task was used, as described and validated before (Kikkert et al., 2017). Participants were instructed to sequentially oppose each of the four fingertips to the approximated tip of their thumb, starting with the index finger. Each participant was asked to perform five repetitions of this movement cycle and to verbally indicate the end of each cycle. Participants first performed the task with their intact hand followed by their phantom hand. Emphasis was given to making (or attempting to make) 'actual' instead of 'imagined' phantom hand movements (Raffin, Giraux, et al., 2012; Raffin, Mattout, et al., 2012; Reilly et al., 2006). During task performance, participants were instructed to keep their eyes closed and keep other body parts still. RT was measured based on participants' verbal reports when completing five movement repetitions. One amputee could not perform the task with their phantom limb, due to complete immobility of their phantom fingers, and was excluded from this task. As none of the congenital one-handers reported experiencing phantom-like sensations, they did not participate in this task.

1.2.4 Prosthesis usage

To assess daily prosthesis usage, we utilised a compound measure that represents both the incorporation of the prosthesis in daily activities and prosthesis wear time, based on methods described by (van den Heiligenberg et al., 2017). The Prosthesis Activity Log (PAL) is calculated from participants' ratings on how frequently they use their prosthesis in an inventory of 27 daily activities (e.g., taking money out of wallet, zipping up a coat, etc.). To calculate prosthesis total wear time, participants rated (on a given scale) how much time they typically spend wearing their prostheses in their daily lives. Both the PAL and maximum wear-time ratings were standardized using a Z-transform and summed to create a compound prosthesis usage score. Note that PAL and prosthesis wear time ratings highly correlate with each other, as previously described by (Van Den Heiligenberg et al., 2018).

1.2.5 Correlation analysis

To test for the role of active visuomotor experience, amputees' age at amputation was correlated (using a Spearman correlation) with mean RTs for images of both hands (see Results) and each hand individually (see Supplementary Figure S3). To test whether current motor control relates to performance in a visual bodily judgement task, this analysis was repeated with mean RTs of phantom hand finger-tapping. These two variables were chosen based on the study's main research question, and in an effort to limit the number of comparisons. A non-parametric Spearman correlation was used for the phantom hand motor control measure because the data did not meet assumptions of normality, as assessed using the Shapiro-Wilks test. To compare the correlation of motor control with that of active visual experience (age at amputation), we conducted a one-tailed test of the difference between two dependent correlations with one variable in common (Lee & Preacher, 2013). In addition, we also conducted exploratory analyses to account for the role of prosthesis usage, previously suggested to impact the reaction time during laterality judgements (Guo et al., 2017; Nico et al., 2004). To allow for additional post-hoc exploration of the results, the complete dataset will be available online, in the project's OSF entry (https://osf.io/b4qks/). With that final analysis as an exception, all other analyses were performed using SPSS software (24.0).

1.2.6 Computational simulation

To explore the potential advantages of parallel bimanual processing during visual laterality judgements (see Discussion), we postulate a covert visuomotor hand posture simulator, accumulating evidence to determine the identity of the hand image stimulus. For a detailed description of the model's algorithm and architecture see Results. Model simulation was performed using Matlab (R2017a). Hand posture simulators were based on a DDM code adapted from (Moran et al., 2016) with an addition of a logarithmic quit-timer.

We chose a drift diffusion model (DDM) to model the hand simulators as they have been extensively used to model cognitive processes involving two-choice decisions where evidence is accumulated over time (Ratcliff & Mckoon, 2008). While in theory a single DDM could have been used to model this task (with each boundary representing a decision threshold for one of the hands), in practice, we were unable to reproduce the response pattern observed in congenital one-handers using this approach. A start-point bias would predict a difference in accuracies accompanied by opposite differences in RTs, which does not fit the pattern we observed in the data for congenital one-handers. As such, in the present study we used two independent DDMs to simulate bimanual visuomotor representation.

The DDM component of the hand posture simulator has the following parameters: bias, threshold, drift-rate and nondecision-time. In addition, for each trial in each hand posture model, a quit-time is drawn from a logarithmic distribution with a mean of T_mu and a sigma of 1s. The 5 parameters were manually optimised to fit the group-level RT and accuracy averages as the task was not designed for a single-subject model fit. For each group, 100,000 trials were simulated (50,000 for each hand). Averages of accuracy and RTs for correct trials are then calculated for each hand. The simulation code can be found on: https://github.com/ronimaimon/HandLateralityModel.

1.3 Results

Mean accuracies and RTs for each viewed hand (intact/missing) and group (controls, congenital one-handers, amputees) are shown in Figure 1.1B and for each difficulty (easy/hard; based on performance of an independent control group on the same task) and group in Figure 1.1C.

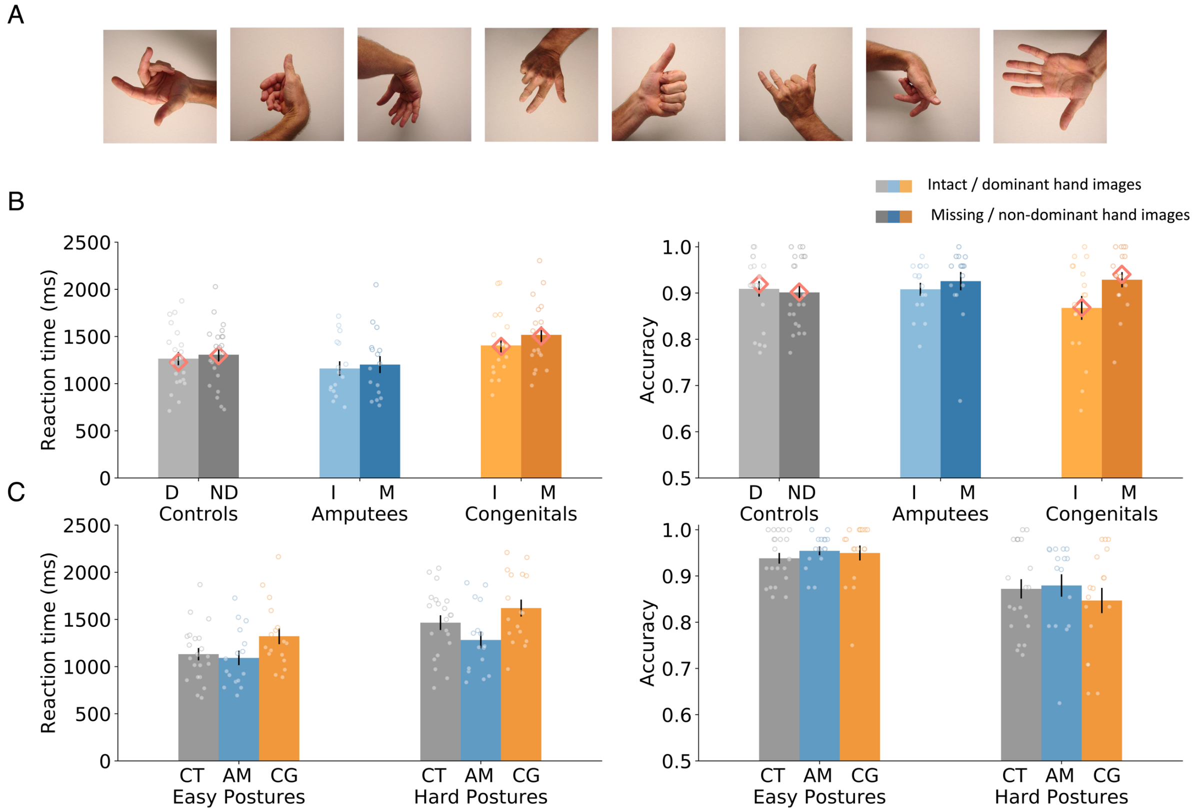

Figure 1.1. *Hand laterality judgment stimuli and results.* (A) Example stimuli used in the hand laterality judgement task. (B) Group performance (absolute RT, left; Accuracy, right) in the hand laterality judgement task is shown for controls (grey), amputees (blue) and congenital one-handers (orange) for the intact and missing hands (light vs dark shades, respectively). Dots correspond to individual performance. (C) Group performance (absolute RT, left; Accuracy, right) in the hand laterality judgement task is shown for easy and hard postures in controls (grey), amputees (blue) and congenital one-handers (orange). Values indicate means ± standard error. Congenital one-handers exhibit slower

RTs in hard postures compared to controls. Congenital one-handers, but not amputees and controls, also show an accuracy difference between the two hands. For RT, absolute RT values are plotted, however all statistical analyses were performed on log-transformed RT values (see supplementary Figure S5 for plots with log-transformed RT values). Pink diamonds depict the predicted performance values from the computational model. CT=controls, AM=amputees, CG=congenital one-handers; D = dominant side images, ND = non-dominant side images; I = intact side images, M = missing side images.

1.3.1 Accuracy

The rmANCOVA analysis of accuracy data revealed a significant interaction between hand and group ($F_{(2,50)}$=3.92, p=0.026), we did not observe a significant main effect of hand ($F_{(1,50)}$=0.70, p=0.41), group ($F_{(2,50)}$=0.29, p=0.75), or a three-way interaction of group, difficulty and hand ($F_{(2,50)}$=0.86, p=0.43; For a full description of all remaining nonsignificant results see Supplementary Table S3; for similar results using a trade-off measure RT/Accuracy, see Supplementary Table S4). These results indicate that hand-loss impacts correct task performance, particularly for the intact hand, but independent of posture difficulty (Figure 1.1B&C, right). Post-hoc hand comparisons within each group confirmed that congenital one-handers show lower accuracy when judging the laterality of intact hand images compared to their missing hand ($t_{(16)}$=3.24, p=0.005). No significant hand differences were observed for controls ($t_{(20)}$=-.491, p=0.629) or amputees ($t_{(15)}$=0.934, p=0.365). Additionally, one extreme outlier was identified in the amputees' group for hard missing hand images. Repeating the analyses above, when removing this outlier, we still find no differences to our results.

A possible intuitive explanation for this pattern of lower accuracy for the intact hand originates from the nature of the decision-making process in the task: when uncertain about the laterality of the image, congenital one-handers may prefer to guess that they are observing a non-familiar (missing hand) posture. This will not impact or slightly increase the accuracy of the missing hand, while reducing accuracy for intact hand postures. To explore this interpretation, we applied Signal Detection Theory, allowing us to dissociate between response bias (criterion) and discriminability (*d'*). No group differences were found in the d' index ($F_{(2,54)}=0.04, p=0.96$; see Figure S4A), indicating all groups were able to discriminate the intact hand images from the missing hand images similarly. However, a one-way ANOVA of *c* criterion values, a measure of bias, revealed significant differences between groups ($F(_{2,54)}=3.31$, $p=0.04$; see Supplementary Figure S4B). While controls showed no bias (*c* was close to 0), congenital one handers' criterion was significantly greater than controls ($t_{(36)}=-2.59$, $p=0.01$) suggesting that congenitals have a bias to assume images are of their missing hand side, while amputees were not significantly different from controls in their criterion ($t(_{35)}=-1.41, p=0.17$).

1.3.2 Reaction Times

The rmANCOVA of reaction times confirmed previous observations (Parsons, 1987, 1994), with a main effect of difficulty with faster RTs for easy vs hard postures across hands and groups ($F_{(1,50)}=18.30$, $p<0.001$). Second, supporting our hypothesis that limited visual and motor experience should result in a difference in RTs across the three patient groups, our analysis showed a significant interaction between difficulty and group ($F_{(2,50)}=4.70, p=0.014$) and a significant group effect ($F(_{2,50)}=3.23$, $p=0.048$). The three-way interaction of group, difficulty and hand was not significant ($F_{(2,50)}=1.63, p=0.21$; see Supplementary Table S2 for a full description of all other nonsignificant results), indicating that changed performance did not depend on the laterality of the hand, with respect to the amputation/missing hand side.

To further explore the group by difficulty interaction, we ran a post-hoc analysis using a one-way ANCOVA (with group as a fixed effect and age as a covariate). This analysis showed that group differences were significant for hard postures ($F_{(2,50)}=3.77, p=0.03$), but only borderline significant in easy postures ($F_{(2,50)}=2.79, p=0.07$). These results indicate that hand-loss impacts performance on the task, particularly for difficult postures, but independent of the laterality of the presented hand (Figure 1.1B&C, left). Exploring the effect of group in RTs of hard posture even further, we found significant differences between congenital one-handers and the other two groups ($F_{(1,51)}$=4.62, p=0.036), further reflected in a significant pairwise difference between congenital one-handers and the amputees group alone ($F_{(1,30)}$=7.62, p=0.01), but not for congenital one-handers compared to controls ($F_{(1,35)}$=1.6, p=0.21). Importantly, no RT differences were found when we tested a subset of our participants (43 out of 54) on a control visual category naming task involving the same setup, confirming no general deficits in verbal RT for congenital one-handers (BF_{10}= 0.18; using a Bayesian ANCOVA; see Supplementary Methods and Figure S2).

We also explored the present data to identify consistency with previous reports for RT differences in congenital one-handers for judging laterality for intact versus missing hands (Funk & Brugger, 2008). A one-sample t-test confirmed a replication of these previous findings, with congenital one-handers performing significantly more slowly when presented with images of their missing hand, compared to their intact hand ($t_{(16)}$=-3.028, p=.008).

1.3.3 Correlation with phantom hand motor control and amputation age

To determine the unique role of present non-visual motor control, we correlated amputees' phantom hand RT during a motor finger-thumb opposition task [as validated in (Kikkert et al., 2017)] with mean RT in the hand laterality judgement task. To explore the role of past active visuomotor experience on hand laterality judgments, we also correlated amputees' age at amputation (reflecting the amount of time individuals had to accumulate visuomotor hand experience) with hand laterality judgement performance. We found a strong correlation between hand laterality performance and phantom hand motor control ($r_{s(13)}$ = 0.695, p=0.004, Figure 1.2), but not with age at amputation (r_s(14) = 0.174, p=0.52, Figure 1.2; see Supplementary Figure S4 for similar results using RTs for intact and missing hand images separately). This result indicates that better motor control of the phantom hand relates to faster hand laterality judgements. The correlation of phantom motor control with RTs of laterality judgments also remained significant after accounting for participants' tapping RT with their intact hand (see Supplementary Results). Since amputees' phantom experience doesn't have a visual domain, we consider this as strong evidence towards the involvement of motor representation in hand laterality judgments. Furthermore, present motor experience (phantom motor control) was found to be a better predictor for laterality judgement performance than previous active visuomotor experience (age at amputation), using a difference test between two dependent correlations with one variable in common (z=1.8, p=0.036).

Finally, as an exploratory analysis, we also examined the potential link between prosthesis usage (Guo et al., 2017; Nico et al., 2004) and RT performance. We found no correlation between prosthesis usage and mean RT on the laterality task for all study participants with a missing hand ($r_{s(31)}$=.018, p=0.922), the amputee group alone ($r_{s(14)}$=-.285, p=0.303) or the congenital group alone ($r_{s(15)}$=-.016, p=0.953). These findings suggest that prosthesis usage does not strongly inform task performance.

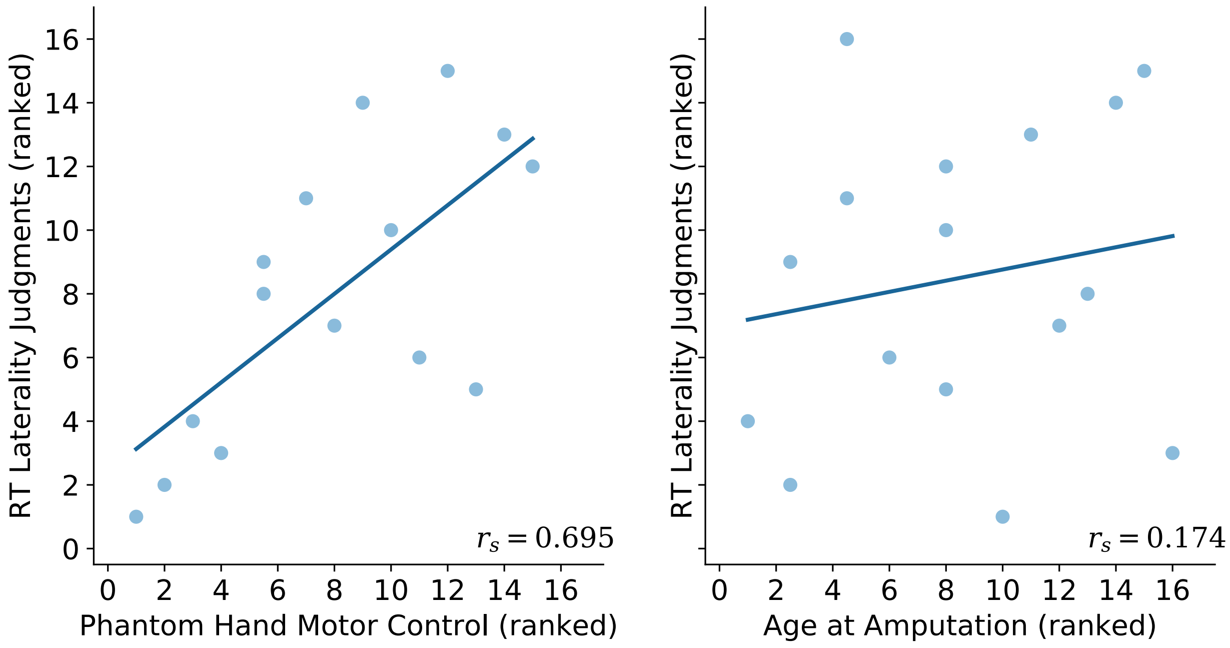

Figure 1.2. *Amputees phantom hand motor control correlated with hand laterality judgement performance.* Mean RT (ranked) for laterality judgements (both intact and missing hand images) is significantly correlated to RTs (ranked) in the phantom hand motor control, $r_s(13)=0.695$, $p=0.004$. This suggests that existing motor control, rather than visual experience, relates to laterality judgements. Smaller values on the phantom motor task denote faster RTs while executing sequential finger-thumb oppositions with the phantom hand. Age at amputation does not correlate with RT for laterality judgements, $r_{s(14)}=0.174$, $p=0.52$. A direct comparison between the correlation revealed there is a significant difference between the two correlations. Thus, for amputees, motor control of the phantom hand is a better predictor of performance on the laterality task than the lack of visual experience of the missing hand.

1.3.4 Computational model simulation

To test our interpretation of the potential advantages of parallel bimanual processing during visual laterality judgements (see 1.4 Discussion), we constructed a post-hoc exploratory simulation, designed to describe a single mechanism that results in the observed error and RT differences between congenital one-handers and controls. We implemented two simultaneous posture simulation processes (one for the left and one for the right hand in controls) to determine whether the seen visual hand posture could be generated using the simulated hand. Conversely, congenital one-handers who only have active visuomotor experience from one hand will deploy a single hand posture simulator. For simplicity, acquired amputees were not included in this simulation, as the model aims to represent a mean observer from each group, and the nature and quality of phantom hand motor control varies across amputees. Moreover, since amputees have residual motor control, they do not provide a compelling test-case for this specific model, beyond the control group.

The model consists of hand posture simulators (based on Drift Diffusion Models) with the addition of a timer component (See Figure 1.3). Each hand posture simulator represents a single hand and accumulates either positive evidence confirming that the posture displayed in the image can be replicated with its hand or negative evidence rejecting that possibility with a drift rate of 0.1. Evidence is accumulated until a threshold is reached, indicating satisfactory information has been gathered to make a decision. Each hand posture model has a starting position between the two thresholds. To generate the slight hand effect [showing faster RT for the intact/dominant hand (Parsons, 1987)], a bias (z=0.006) was set towards the intact/dominant-hand in both hand posture simulator (i.e. an equal negative bias was set in the non-dominant hand posture simulator). Since some postures might be particularly awkward or difficult to replicate, a timer was added to avoid conceptually long exhaustive evidence accumulations. If the quit-time elapses before enough evidence was accumulated to reach a decision, the hand posture model returns a 'reject' decision, meaning it has concluded that the posture cannot be replicated with its hand. In other words, we allow a hand posture model to say: 'I give up, it's not this hand'. For each trial a quit-time is drawn from a logarithmic distribution with a mean of 1.6s and a sigma of 1s. RT is determined by the time it took the hand posture simulator to reach a decision with the addition of a non-decision time (=0.3s) to account for early-processing and response-generation processes. Finally, since both groups are working under the same time pressure (dictated by the quit timer), and since congenital one-handers are slower in their RT, to maintain the same level of accuracy they would need to lower their evidence threshold (*controls-threshold*=.17 and *congenitals-threshold*=.138). This strategy adjustment was made to allow the congenital one-handers to cope with the single simulator situation.

In controls, the model consists of two hand posture simulators, one for each hand, gathering evidence in parallel on whether the viewed hand posture in each trial is of the hand they represent or not. The model that reaches a decision first will determine the trial's response (the identity of the displayed hand) and RT. In congenital one-handers, only a single hand posture simulator for their intact hand is present. Here, a "dominant-hand" response (e.g., right hand in the example in Figure 1.3) will be the result of the right-hand posture model accumulating evidence in support of the stimulus being of a right hand. While a “nondominant-hand” response will either be: (1) a result of evidence accumulated against the right-hand until rejecting the possibility the viewed posture can be replicated with the right-hand, thus responding “left-hand”. Or (2) accumulating evidence without crossing the evidence threshold, reaching the quit-time, and rejecting the right-hand hypothesis. The simulation has successfully replicated both RT and accuracy group patterns observed in the empirical group results (see pink diamonds in Figure 1.1B).

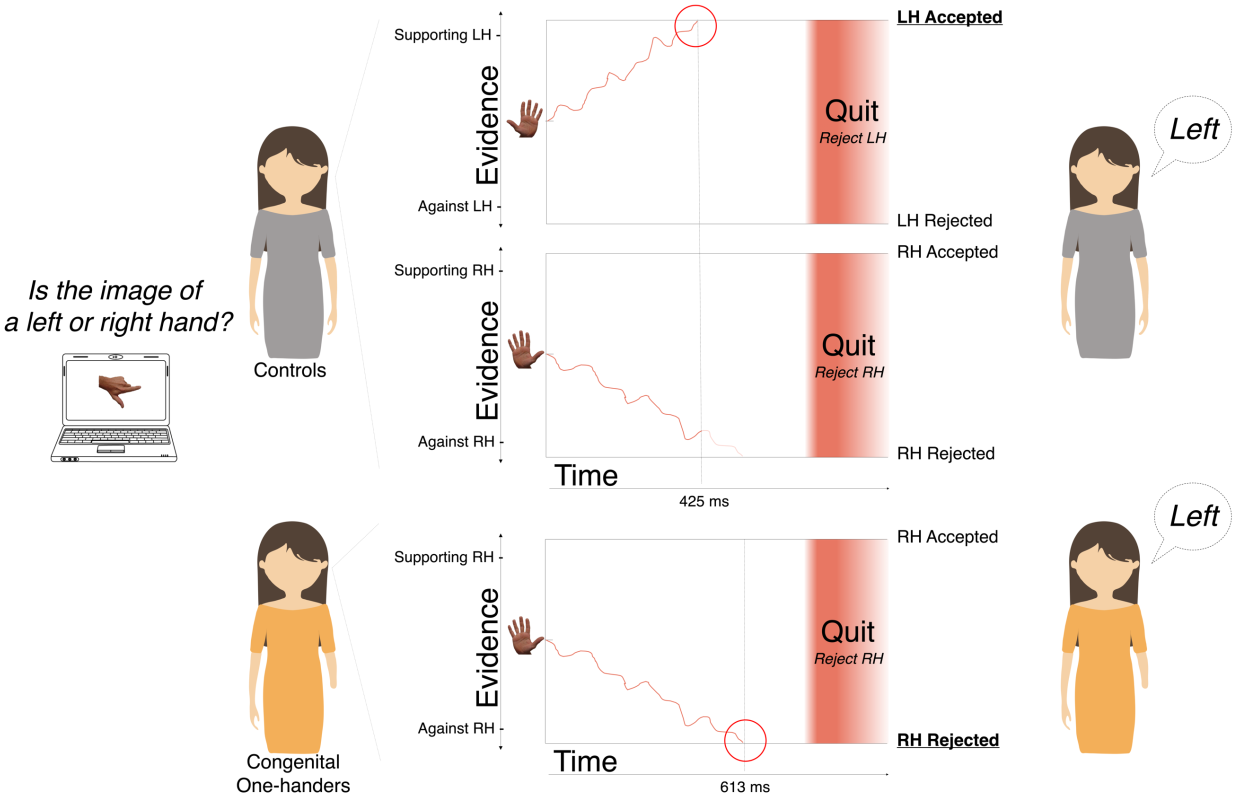

Figure 1.3. *A schematic diagram illustrating the laterality decision making process as simulated by our computational approach.* The top panel illustrates a decision process example in a two-handed control (depicted as the woman in the grey dress). In response to the hand image stimulus, left- and right-hand posture models are simultaneously activated, each collecting evidence to either accept or reject whether the hand posture in the stimulus could be generated with that hand. In the example above, once enough evidence is collected by the left-hand posture model to accept that the visual hand posture can be generated by the left hand, the two-handed individual (correctly) judges the hand stimuli as a left hand. Because the actual stimulus is left, the drift rate is positive and negative for the left- and right-hand simulators, respectively. Once the left-hand model collected enough evidence to reach the decision threshold, the right-hand model abandons its process. The bottom panel illustrates the process in

response to the same visual stimulus in a right-handed congenital (orange dress). In this example, we illustrate how having a single hand posture model can be less efficient and result in slower reaction times. Since this individual never had visuomotor experience of a left hand, we assume this individual can only utilise a single right-hand posture model to judge hand laterality. In the example above, the right-hand model takes longer to reach the decision threshold, to conclude the presented posture cannot be generated with the right hand. Note that if sufficient evidence had not been collected to reach a decision before the quit timer, then a "reject" decision would be forced.

1.4 Discussion

It has been suggested by philosophers that our interactions with the environment may play a fundamental role in the development of our perceptual and cognitive abilities. According to this premise, termed 'embodied cognition', body representation may play an important role in shaping cognition. While this view is gaining increasing popularity both in philosophy (Shapiro, 2019), psychology (Fossataro et al., 2018; Garbarini & Adenzato, 2004; Martinaud et al., 2017; Wilson, 2002) and even in engineering (Metta et al., 2008), it still awaits further empirical evidence. In particular, previous studies highlighted the influence of motor disorders on performance on the hand laterality judgement task (Conson et al., 2010, 2013; Fiorio et al., 2006; Helmich et al., 2007; Nico et al., 2004). However, this interpretation was confounded by the ecological pairing of visual and motor experience. As such, an alternative interpretation highlighting the reliance on visual experience (Vannuscorps et al., 2012; Vannuscorps & Caramazza, 2015, 2016), and in particular first-person (active) visual experience, cannot be ruled out based on existing evidence. In the present study, we aimed to disentangle the potential contributions of active (self) motor experience from passive visual experience (of others), by studying three groups of individuals with inherently different hand experiences (see Table 1.1). Our experimental design, involving one-handers with congenital and acquired hand-loss, combined with an evaluation of phantom hand motor control, allowed us to demonstrate that current motor control is a driver in making bodily judgments.

First, we show that congenital one-handers make increased judgment errors for images of their intact hand compared to their missing hand. This counterintuitive finding was previously observed in three congenital one-handers tested in Nico et al., 2004. However, due to the limited sample size, the authors were unable to interpret this finding. Additionally, we show that individuals born with one hand are less effective at judging difficult hand postures' laterality, in terms of RT profile, than individuals who lost a hand in adult life. The significant difference from amputees rules out the contribution of current visual information on hand laterality judgements and supports a role of either previous visuomotor experience or current motor experience on task performance.

Our reported correlation of amputees' phantom hand motor control, and not duration of experience with a limb (age at amputation), with visual laterality task performance, provides strong evidence for the role of currently available motor resources when making bodily judgments, supporting the notion of 'embodied cognition'. Phantom hand motor control has been shown to rely on preserved neural resources across the sensorimotor system (Bruno et al., 2019; Bruurmijn et al., 2017; Garbarini et al., 2018; Kikkert et al., 2016; Raffin et al., 2016; Raffin, Mattout, et al., 2012; Reilly et al., 2006), and the task used in the current study has been previously related to persistent sensorimotor activity for the missing hand at the peripheral (Raffin, Giraux, et al., 2012) and cortical levels (Kikkert et al., 2017). As phantom movements have no visual attributes, studying motor control of the phantom hand provides a unique opportunity to examine the specific contributions of motor processing. Furthermore, our findings also demonstrate that phantom hand motor representation, previously considered as a remnant of the sensorimotor system (Kikkert et al., 2016), potentially related to phantom limb pain (Kikkert et al., 2017, 2018) can be actively utilised to inform body-representation judgements.

The present results showing divergence in hand representation between congenital one-handers and amputees, which showed similar performance to controls, and the suggested role for motor representation in accounting for these differences, is consistent with recent research into brain plasticity subsequent to hand loss. The few functional MRI studies considering plasticity in visual hand representation so far reported no differences between congenital one-handers and acquired amputees (Van Den Heiligenberg et al., 2018), and between individuals with congenital hand loss and controls (Maimon-Mor et al., 2017; Striem-Amit et al., 2017). This is likely related to the fact that even when considering hand-selective areas, the visual cortex in individuals with a missing hand is not deprived in a strong sense. Conversely, when studying hand representation in primary somatosensory and motor cortex, multiple recent evidence demonstrates that amputees (for review see Makin & Bensmaia, 2017), but not congenital one-handers (Wesselink et al., 2019), show typical sensorimotor representation of their missing hand despite amputation. Instead, congenital one-handers show robust remapping of multiple body-part representations into their missing hand sensorimotor area (Hahamy et al., 2017, 2015; Hahamy & Makin, 2018; also see Striem-Amit, Vannuscorps, & Caramazza, 2018 for evidence of cortical remapping in individuals born without both hands). The extent of this remapping spans well beyond other recent reports for remapping in acquired amputees, which has been shown to be mostly restricted to the intact hand (Makin, Cramer, et al., 2013; Philip & Frey, 2011; Raffin et al., 2016). Collectively, this evidence indicates that amputees have more neural resources than congenital one-handers for updating sensorimotor, but not visual, hand representation, which could contribute to the group similarities and differences in visual laterality judgement revealed in the current study.

As mentioned above, congenitals diverged from the other two groups in terms of error rates, and under some circumstances (particularly when judging challenging hand postures) also showed increased reaction times (e.g., compared with controls and acquired amputees put together). Previous studies demonstrated that congenital one-handers were slower and less accurate bilaterally in a motor-planning task, compared with two-handed controls (Philip et al., 2015), while amputees showed no significant differences from controls (Philip & Frey, 2011). An interesting possible interpretation for the diverging response patterns in congenital one-handers compared to controls and acquired amputees is that they only have a single intact-hand motor representation compared to two hand representations in controls. This account stems from contemporary views of motor planning and action selection (Cisek, 2007; Cisek & Kalaska, 2010; Klein-Flügge & Bestmann, 2012; Oliveira et al., 2010), where each potential action is refined simultaneously until enough evidence is collected in favour of one action over the others (Cisek & Pastor-Bernier, 2014). To explore this interpretation, we constructed a computational simulation for the congenital one-handers group and control group (see Figure 1.3). The simulation has successfully replicated both accuracy and RT group patterns observed in the empirical group results (see pink diamonds in Figure 1.1B). The surprising effect of lower accuracy for congenital one-handers intact hand is a result of a single simulator with a single quit timer, generating overall more “missing hand” than “intact hand” responses. In controls, having two simulators means similar likelihood for each to reach the quit time, resulting in a more balanced laterality accuracy pattern. The slower (albeit non-significantly so) RT effect with congenital one-handers was induced due to the existence of two parallel simulators in controls vs one in congenital one-handers: since the decision is made by the simulator that reaches the decision threshold first, having twice as much evidence will speed up the convergence on a decision in controls. As such, the number of hand posture models can potentially account for the observed differences between controls and congenital one-handers in the laterality judgement task. We therefore suggest that a bimanual sensorimotor system is more effective than a unimanual system in visual bodily judgements.

In our computational simulation, we equipped the two accumulators for the control group with identical parameters, discounting the potential role of handedness in informing motor decisions (de Lange et al., 2006; Gentilucci et al., 1998; Sekiyama, 1982; Takeda et al., 2010). However, previous studies suggesting that amputation impairs performance on visual laterality tasks were carried in amputees missing their (formerly dominant) right hand (Guo et al., 2015, 2017; Lyu et al., 2016, 2017), with amputees with non-dominant hand amputation showing no differences in performance compared to able-bodied controls (Nico et al., 2004). In the present study, we prioritised recruiting amputees missing their left hand (to control for missing hand side in congenital one-handers, which is predominantly left), resulting in a majority of amputees missing their non-dominant hand (*n*=12). As such we are unable to comment on the role of motor laterality (as induced by either hand dominance or physical side) on the process of visual laterality judgements. Therefore, our preliminary simulation is exploratory, and awaits further confirmatory evidence and refinement.

In the present study, we focused our investigation on the relationship between visual laterality judgement and preserved motor control, though other factors might also be important contributors to laterality performance. For example, previous evidence is conflicting as to the impact of prosthesis use on visual laterality judgements of simple postures. Nico and colleagues (2004) first showed that amputees that regularly wear a prosthesis had decreased performance (both in terms of RT and accuracy) compared to amputees that do not wear a prosthesis and able-bodied controls. Alternatively, Guo et al., 2017 reports an opposite result suggesting that prosthesis usage actually ‘normalises’ the motor body representation (body schema) and therefore facilitates RT in the laterality task (see Schwoebel & Coslett, 2005 for evidence in stroke patients that characterises multiple, distinct body representations, see Heed & Röder, 2012 for a discussion of the role of the body schema in multisensory processing, and de Vignemont, 2010 for a conceptual analysis of the body schema and the body image). Unlike the simplistic postures of the hand image stimuli used by Nico, Guo and colleagues, prostheses do not afford the complex hand configurations we explore in the present study's stimuli set. Therefore, prosthesis use does not necessarily provide useful information for the present task, potentially explaining the lack of correlation between prosthesis usage scores and mean RT on the laterality task for all our study's participants with a missing hand or the congenital and amputee groups alone.

These results potentially have further implications on the design of prosthetic arms. Aspiring to better mimic the hand, advanced motorised prosthetic arms designs require complex control schemes. This complex level of control is often highly dependent on the user's ability to generate complex signals (usually based on different intended hand movements). In other words, this approach relies on the user's existing biological hand or hand-like control infrastructure. This highly disadvantages congenital one-handers considering the accumulating evidence for their lack or decreased hand-related infrastructure in some respects (Wesselink et al., 2019) and the dependency on early-life experience in others (Chapter 3). Even within the acquired amputees' population, a vast range of phantom-limb mobility has been recorded making this approach somewhat problematic.

Put together, we offer multiple evidence for impaired visual laterality judgement in individuals with congenital hand loss, as summarised in our signal detection analysis and computational simulation. This converging evidence is at odds with recent results of 'typical' bodily judgment performance in individuals born without both hands (Vannuscorps et al., 2012; Vannuscorps & Caramazza, 2015, 2016). As mentioned in the introduction, these previous studies provided evidence for convergent processing of visual hand information independent of congenital hand loss, paving the way to the view that visual body representation can be entirely divorced from motor experience. One potential explanation of this conflict is that passive observation alone might be enough to develop a limited model of the biomechanical properties of hands, but this model is insufficient to support an extended repertoire of motor control. For this reason, the stimuli used in our study portrayed high biomechanical complexity, also involving postures and angles that are not typically available through passive visual experience. Another possible reason for the discrepancies between the results in congenital one-handers compared to the individuals with bilateral hand absence is the limited sample sizes used in the latter studies (*n*=1-5), resulting in low statistical power, used sometimes in support of the null hypothesis.

In summary, visual information is known to be an influential driver for informing and guiding motor control, as shown in behavioural studies (Honda, Hirashima, & Nozaki, 2012; Saunders, 2004), computational models (Körding & Wolpert, 2004) and in clinical populations (Archer et al., 2018). In the present study, we explored the driving role of motor experience in shaping visual perception and cognition. Specifically, we aimed to gain a better understanding of the role of motor representation in influencing visual bodily judgments. We propose that, when available, motor hand representation is a resource used together with the visual system to optimise hand laterality judgments. Our results provide a novel framework for the process of 'embodied cognition', which should be considered in future endeavours for creating neurocognitive-inspired artificial motor or visual systems.

Chapter 2 | Is an artificial limb embodied as a hand? Brain decoding in prosthetic limb users

Adapted from:

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Chapter Abstract

The potential ability of the human brain to represent an artificial limb as a body-part (embodiment) has been inspiring engineers, clinicians and scientists as a means to optimise human-machine interfaces. Using fMRI, we studied whether neural embodiment actually occurs in prosthesis users' occipitotemporal cortex (OTC). Compared with controls, different prostheses types were visually represented more similarly to each other, relative to hands and tools, indicating the emergence of a dissociated prosthesis categorisation. Greater daily-life prosthesis usage correlated positively with greater prosthesis categorisation. Moreover, when comparing prosthesis users' representation of their own prosthesis to controls' representation of a similar looking prosthesis, prosthesis users represented their own prosthesis more dissimilarly to hands, challenging current views of visual prosthesis embodiment. Our results reveal a use-dependent neural correlate for wearable technology adoption, demonstrating adaptive use-related plasticity within the OTC. Since these neural correlates were independent of the prostheses' appearance and control, our findings offer new opportunities for prosthesis design, by lifting restrictions imposed by the embodiment theory for artificial limbs.

2.1 Introduction

The first challenge in harnessing the potential powers of embodiment to improve prosthesis design and usage is measuring embodiment. To measure embodiment, we must first define it, as the word embodiment is often used interchangeably to describe a wide range of phenomena. From a neural standpoint, embodiment is defined by the successful allocation of brain resources, originally devoted to controlling one's own body, to represent and operate external objects (de Vignemont, 2011). Here we focus on visual neural embodiment — the successful allocation of visual hand-related neural resources. Visual embodiment is particularly relevant for studying prosthesis representation, this is because prosthesis usage is highly visually guided (Antfolk et al., 2013). Moreover, visual internal models of the body have been suggested as essential gateways for processing multisensory integration that will result in for successful bodily ownership (Tsakiris, 2010), a desired feature of prosthesis usage (Beckerle et al., 2018; Giummarra et al., 2008). Previous efforts to test visual prosthesis embodiment using the rubber hand illusion did not associate it with improved prosthesis usage (Collins et al., 2017; D'Alonzo et al., 2015; Ehrsson et al., 2008; Marasco et al., 2011; Mulvey et al., 2012; Rognini et al., 2019; Rosén et al., 2009; Schmalzl et al., 2014; though see Graczyk et al., 2018 for results from two individuals). We have recently found that as a whole, one-handed individuals tend to respond neutrally to embodiment statements in relation to their own prostheses (Appendix C). Moreover, these measures of embodiment tend to rely on an explicit sense of body ownership on the phenomological level, which might not be a necessary consequence of implicit neuronal embodiment (i.e., reallocation of body-part resources to represent or control the prosthesis (de Vignemont, 2011)).

As a more direct means of measuring neural visual embodiment, or how the brain represents prosthetic limbs, a recent study assessed activity levels in prosthesis-users' occipitotemporal cortex (OTC) while participants were viewing images of prosthetic limbs, using functional MRI (fMRI) (Van Den Heiligenberg et al., 2018). The OTC is known to contain distinct visual representations of different object categories (Kriegeskorte et al., 2008), for example: hands (Bracci et al., 2015; Orlov et al., 2010), tools (Bracci & Peelen, 2013), faces (Tsao & Livingstone, 2008), and bodies (Downing & Peelen, 2016). It was previously shown to contain overlapping visual and motor body-part selective representations (Astafiev et al., 2004; Orlov et al., 2010), and even responds to touch (Beauchamp et al., 2009; Tal et al., 2016). OTC has been previously implicated in multisensory integration processing related to embodiment (Gentile et al., 2013; Limanowski et al., 2014; Limanowski & Blankenburg, 2016) and OTC's connectome associates it with hand actions. For example, hand and body-selective visual areas uniquely connect to the primary sensorimotor hand area (Tal et al., 2016). These characteristics qualify the OTC as an ideal candidate for studying action-related visual body-representation. In the study mentioned above, Van Den Heiligenberg and collegues (2018) found that individuals who used their prosthesis more in daily lives also showed greater activity in OTC's hand-selective visual areas when viewing images of prostheses, and greater functional coupling with sensorimotor hand areas (Van Den Heiligenberg et al., 2018). This result demonstrates that prosthesis users are able to engage visuomotor hand-selective areas while passively representing a prosthesis. However, it is yet unknown whether prosthesis visual representation actually mimics that of a hand (i.e. neural embodiment). Alternatively, since the visual hand-selective regions partially overlap with hand-held tool representation (Bracci et al., 2012), the observed activity gains may reflect the prosthesis being represented as a tool. As a third option, since object categorisation in OTC is thought to be based on their semantic and functional properties (Reddy & Kanwisher, 2006), expert prosthesis usage may result in the emergence of prostheses representation as a new 'category', diverging from its existing natural categories (e.g. 'hands', 'tools'). This third alternative is consistent with recent evidence showing that visual expertise can contribute to the shaping of categorical representation in OTC (Gomez et al., 2019) (see 2.3 Discussion).

Brain decoding techniques which take advantage of multivoxel representational patterns allow us to reveal the representational structural underlying fMRI activity, for example, to dissociate overlapping hand and tool representations within the lateral OTC (Bracci & Peelen, 2013; Lingnau & Downing, 2015). Here, we utilised fMRI data of 32 individuals missing a hand, with varying levels of prosthesis usage (hereafter – prosthesis users; see Table 2.1), and 24 two-handed control participants, who have varying life experience of viewing prostheses (See Supplementary Table S1). The OTC's extrastriate body selective area (Downing & Peelen, 2016) was independently localised. Two main hypotheses were tested: the embodiment hypothesis, assessing whether prosthetic limbs are in fact represented visually as hands and not tools; and, the categorisation hypothesis, assessing whether a new 'prosthesis' category has formed. To provide distinct predictions for each of these hypotheses, we studied representational similarities between hand, tools, and upper limb prosthetics images (both cosmetic - designed to resemble hand appearances; and active – designed to afford a grip, e.g. a "hook"; Figure 2.1A) and compared prosthesis users to controls. Broadly speaking, the visual hand embodiment hypothesis predicts that compared to controls, the various prosthesis conditions in prosthesis-users will be more similar to hands than to tools (notice that this prediction also allows us to test the inverse prediction – that prostheses are represented more like tools in one-handers). The categorisation hypothesis predicts that in prosthesis-users, the prosthesis conditions will be more similar to each other relative to hands and tools.

Subject	Gender	Age	Age at Amp	Level of Amputation	Missing Hand Side	Cause	Usage Skill (PAL)	Usage Time			Pros Usage	Own Cond Pros	Own Cond Hand-like
									Active				
								Cosmetic	Mechanical	Myoelectric			
01	M	57	20	Below elbow	Left	Trauma	0.57	5	0	0	2.99	Cosm	1
02	F	49	.	Below elbow	Left	Congenital	0.46	4	0	0	1.92	Cosm	1
03	M	59	40	Above elbow	Left	Trauma	0	0	0	0	-2.42	.	.
04	F	52	.	Below elbow	Right	Congenital	0.15	5	1	0	1.00	Cosm	1
05	M	58	27	Above elbow	Left	Trauma	0.09	5	2	0	.72	Mech	0
06	M	53	28	Below elbow	Left	Trauma	0.24	3	5	0	1.43	Mech	0
07	M	52	.	At wrist	Left	Congenital	0.04	0	3	0	-.60	.	.
08	M	41	27	Above elbow	Right	Trauma	0.09	2	1	0	-.91	Cosm	1
09	M	48	17	Above elbow	Left	Trauma	0	2	2	0	-1.34	.	.
10	F	25	.	At wrist	Right	Congenital	0	0	0	0	-2.42	Cosm	1
11	M	49	.	Above elbow	Left	Congenital	0.26	1	4	0	.98	Mech	1
12	M	37	27	Above elbow	Left	Trauma	0.28	0	2	0	-.01	.	.
13	F	46	38	Below elbow	Left	Trauma	0	0	0	0	-2.42	Cosm	1
14	F	28	.	At wrist	Left	Congenital	0	0	0	0	-2.42	.	.
15	M	64	33	Below elbow	Right	Trauma	0.33	0	2	5	1.85	Myo	1
16	M	38	.	Below elbow	Left	Congenital	0.39	5	0	0	2.14	Cosm	1
17	F	24	18	Below elbow	Right	Trauma	0	0	0	0	-2.42	Cosm	1
18	F	27	.	Below elbow	Left	Congenital	0.54	5	0	0	2.84	Cosm	1
19	M	49	37	Above elbow	Left	Trauma	0	1	0	0	-1.88	Cosm	1
20	M	60	.	At wrist	Left	Congenital	0.06	2	0	0	-1.05	Cosm	1
21	F	34	.	Below elbow	Right	Congenital	0.46	5	0	0	2.47	Cosm	1
22	F	36	.	Below elbow	Right	Congenital	0.57	5	0	0	2.99	Cosm	1

23	F	50	45	Above elbow	Left	Tumor	0	0	2	0	-1.34	Mech	0
24*	F	41	.	Below elbow	Left	Congenital	0.54	0	0	5	2.84	Myo	1
25*	M	29	24	Through shoulder	Left	Trauma	0.09	0	0	2	-.91	Myo	1
27*	M	25	.	Below elbow	Left	Congenital	0.59	1	0	5	3.08	Myo	1
28*	M	34	.	At wrist	Left	Congenital	0.11	0	0	3	-.27	Myo	1
29*	M	25	18	At wrist	Left	Trauma	0	0	2	0	-1.34	.	.
30	M	38	.	Below elbow	Left	Congenital	0	0	2	1	-1.34	Myo	1
31	F	49	.	At wrist	Left	Congenital	0	1	0	0	-1.88	Cosm	1
32	M	45	20	Below elbow	Right	Trauma	0.09	2	0	0	-.91	Cosm	1
33	M	32	31	Above elbow	Left	Trauma	0	0	2	0	-1.34	Mech	0

Table 2.1. *Prosthesis-users' demographic details and daily prosthesis usage habits.* M/F = male/female; Age at Amp. = Age at amputation; PAL = Prosthesis Activity Log scores: how frequently users incorporate their prosthesis in an inventory of 27 daily activities (e.g., taking money out of wallet etc.). Scores of 0 = never, 1 = sometimes, 2 = very often. The sum of all items was divided by the highest possible score, such that individuals were rated on a scale ranging from 0 to 1; Usage Time= Prosthesis wear time for each prosthesis type: 0 = never; 1 = rarely; 2 = occasionally; 3 = daily <4 h; 4 = daily 4–8 h, 5 = daily >8h. Bold marks the user's primary prosthesis; Pros. Usage Score = Prosthesis usage score, a composite measure of prosthesis wear time and skill; Own Cond Pros = The Prosthesis the participant brought on the day of experiment and was shown in the own prosthesis condition. Cosm = Cosmetic, Mech = Mechanical, Myo = Myoelectric; Own Cond Hand-like = relates to the visual appearance of the prosthesis they viewed in the own prosthesis condition. Note that participants 11's prosthesis was a mechanical hook with a glove and is therefore hand-like. Asterisks denote the participants who were presented with a myoelectric prosthesis for the active prosthesis condition

2.2 Results

2.2.1 Clustering of prostheses types in prosthesis-users but not in controls

Analysis was focused on the OTC's extrastriate body-selective area (Downing et al., 2001; Peelen & Downing, 2007). This ROI was independently localised for each participant by choosing the 250 voxels in each hemisphere showing the strongest preference to images of headless bodies over everyday objects (Figure 2.1B).

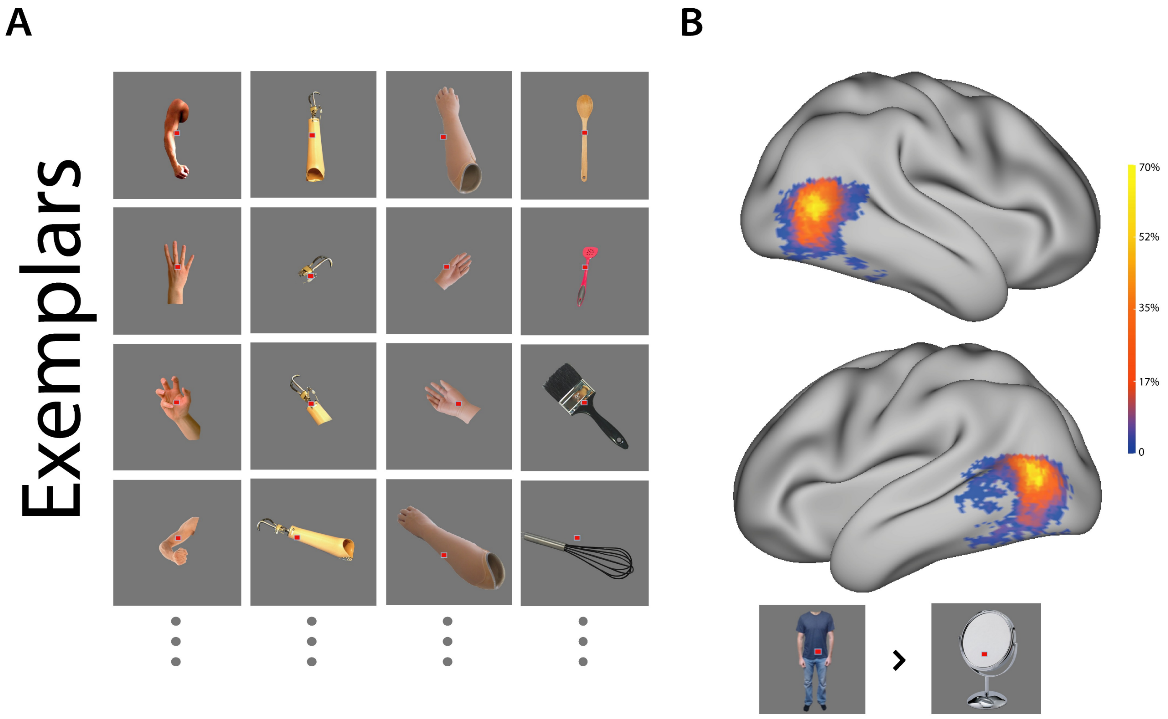


Figure 2.1. *Example stimuli and Region of interest (ROI).* (A) Example stimuli from the main 4 experimental conditions (columns; left-to-right): hands (upper limbs), active prostheses, cosmetic prostheses, hand-held tools. One-handers also observed images from multiple viewpoints of their own prosthesis. One image was shown per trial in an event-related design. (B) Probability maps of the body-selective region of interest. For each participant and hemisphere, the top 250 most activated voxels within the occipitotemporal cortex were chosen based on a headless-bodies > objects contrast, providing an independent ROI. ROIs from all participants (*n*=56) were superimposed, yielding ROI probability maps. Warmer colours represent voxels that were included in greater numbers of individual ROIs. See supplementary Figure S1 for the probability maps of each group separately.

To investigate the underlying representational structure within this region, we first characterised multivoxel activity patterns for each participant and condition (hands, tools, cosmetic prostheses that look like hands and active prostheses that tend to resemble tools rather than hands, Figure 2.1A; all exemplars are available at https://osf.io/kd2yh/). Distances between each pair of activity patterns (e.g. hands and cosmetic prostheses) were calculated (noise-normalised cross-validated mahalanobis distances (Walther et al., 2016)). More similar activity patterns will result in smaller distances, or in other words, the more dissimilar two patterns are, the greater their relative distance is. Since these are multi-dimensional patterns, one way to visualise the structure is using a dendrogram, or linkage tree, which illustrates how the different conditions cluster. Using this method on the average distances for each group, we found qualitative differences in the representational structure between controls and prosthesis users (Figure 2.2). For control participants, cosmetic prostheses were clustered with hands, and active prostheses were clustered with tools, reflecting their native inter-categorical similarities across conditions (see supplementary Figure S2 for visual similarity analysis). For prosthesis users, however, the two prostheses were clustered together, potentially reflecting a newly formed prosthesis category, with tools and hands being further away from both prosthesis conditions.

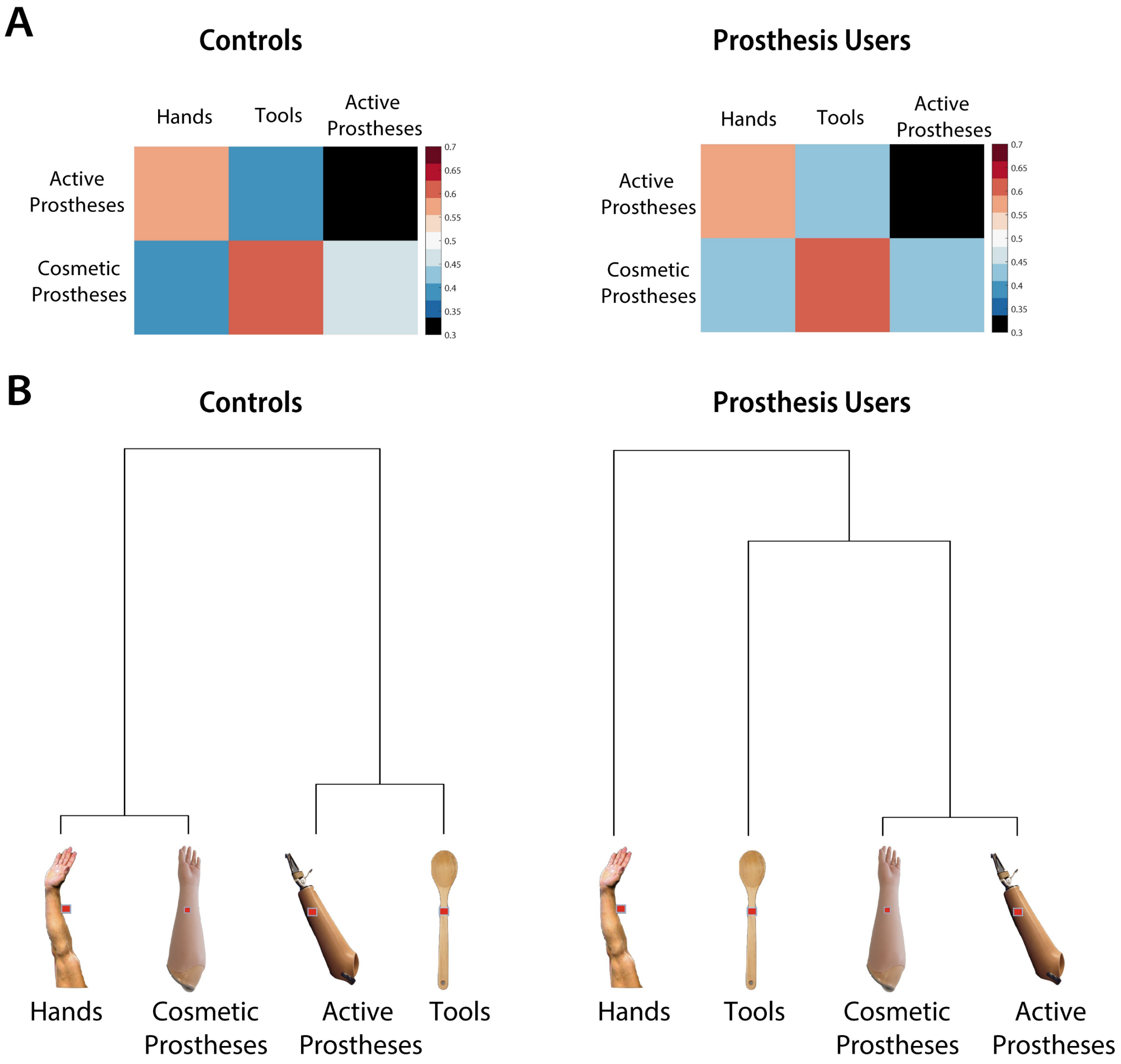


Figure 2.2. *Representational structure in body-selective visual.* Multi-dimensional distances between activity patterns of each of the main condition (hands, tools, cosmetic prostheses, active prostheses) were calculated using representational similarity analysis. (A) Representational dissimilarity matrices for each group showing pairwise distances between the two prostheses conditions (active and cosmetic), hands and tools. (B) To visualise the underlying representational structure a linkage tree (dendrogram) was calculated in each group of participants, combining information from all pair-wise distances (two-handed controls, left; one-handed prosthesis users, right). Pairs of stimuli that are closer together in the multi-dimensional space are clustered together under the same branch. Longer connections across the vertical axis indicate greater relative distances. In controls, cosmetic prostheses are clustered with hands and active prostheses with tools, reflecting their visual similarities. In prosthesis users, however, the two prostheses types (cosmetic and active) are clustered together, with tools and hands represented dissimilarly from both prostheses.

2.2.2 Prosthesis-like (categorical), and not hand-like (embodied) representation of prostheses in prosthesis users

Next, we set out to quantify prosthesis representation, using the two alternative theoretical frameworks – embodiment versus categorisation. According to the embodiment hypothesis, prosthesis representation should resemble hand representation. This hypothesis predicts that in prosthesis-users, each of the two prosthesis conditions will be more similar (smaller distance) to hands than to tools, compared to controls (quantified as a Hand-similarity index, see Methods). Notice that the Hand-similarity index is the inverse of a tool-similarity index. Therefore, significantly negative embodiment should be taken as evidence for association of the prosthesis with a tool. When comparing Hand-similarity indices based on the multidimensional distances across participant groups, we found no significant differences ($t_{(54)}$=0.47, p=0.64; Figure 2.3A). A Bayesian t-test provided substantial evidence in support of the null hypothesis (BF_{10}=0.2), i.e., that on average amputees do not visually represent an unfamiliar prosthesis more similarly to a hand than controls. Similar results were observed across the two hemispheres (Right OTC: $t_{(54)}$=0.46, p=0.65; Left OTC: $t_{(54)}$=0.54, p=0.60).

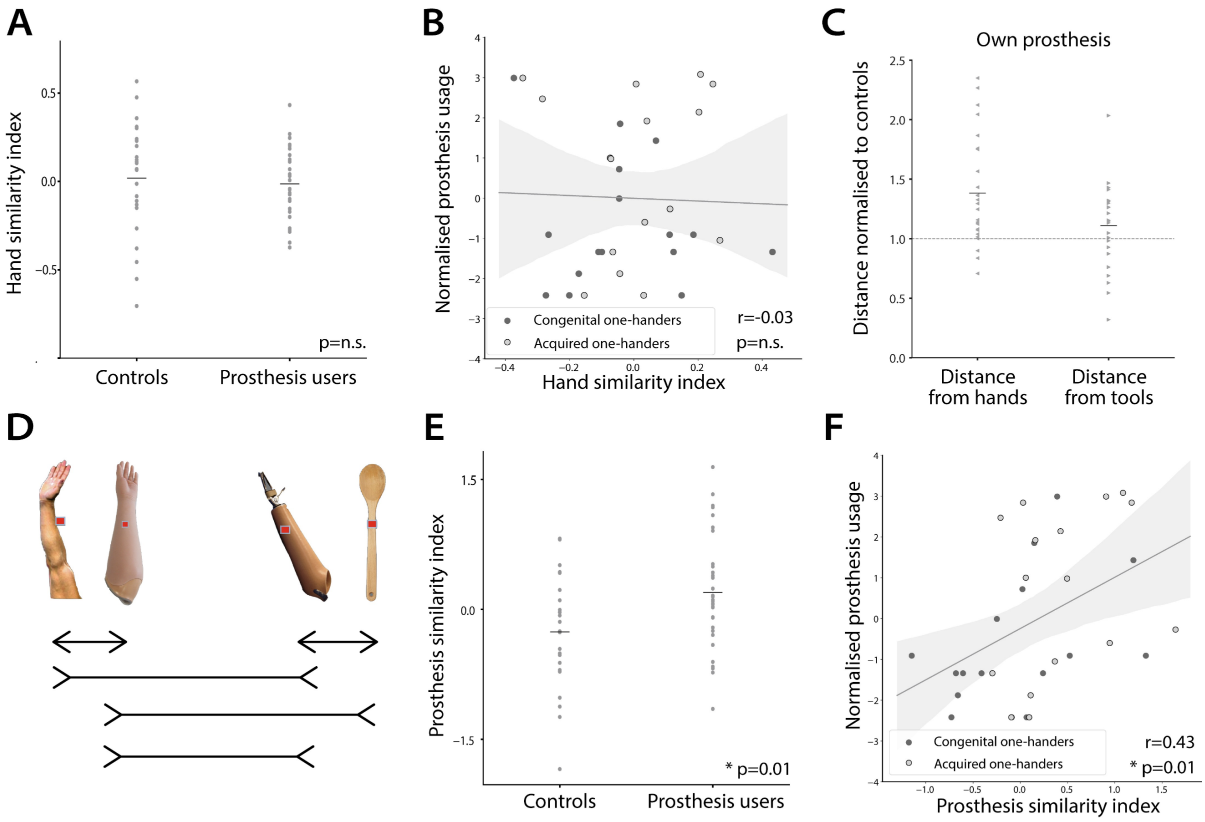


Figure 2.3. *Assessing the embodiment and categorisation hypotheses.* (A-B) A Hand-similarity index was calculated for each participant to quantify the degree to which both prostheses conditions (cosmetic and active) are more similar to hands than tools. A higher index in value indicates greater embodiment (Hand-similarity of prostheses). (A) A group comparison of the Hand-similarity index between controls and prosthesis users showed no significant differences (n.s.) [$t_{(54)}$=0.47, p=0.64]. Horizontal lines indicate group means and dots indicate individual participants. (B) Correlation between the Hand-similarity index and prosthesis usage was not significant across users [*Pearson's* $r_{(30)}$=-0.03, p=0.86]. Dark/light circles indicate congenital/acquired one-handers respectively, and grey shading indicates a bootstrapped 95% confidence interval (C) Hand (left) and tool (right) distances from users' 'own' prosthesis. Individual distances were normalised by the controls' group mean distance, depending on the visual features of the 'own' prosthesis (hand-likeness). A value of one indicates similar hand/tool distance to controls. Users showed significantly greater distances between their own prosthesis and hands [$t_{(25)}$=4.33, p<0.001] contrary to the embodiment hypothesis. Together, these findings demonstrate that Hand-similarity under the embodiment hypothesis does not adequately explain differences in prosthesis representation in users' occipitotemporal cortex. (D-F) A Prosthesis-similarity index was calculated for each participant to quantify the degree to which the prostheses representation moved away from their natural categories (hands for cosmetic prostheses and tools for active prostheses) and towards one another. (D) A visual illustration of the Prosthesis-similarity index formula. Arrows pointing outward indicate distances that should grow in users compared to controls (e.g., hands

and cosmetic prostheses) and are therefore positively weighted. Arrows pointing inward indicate distances that should shrink in users compared to controls (i.e., cosmetic and active prostheses) and are therefore negatively weighted. (E) Group comparison of the Prosthesis-similarity index between controls and prosthesis users showed greater Prosthesis-similarity in users [$t_{(54)}$=-2.55, p=0.01]. (F) The Prosthesis-similarity index significantly correlated with prosthesis usage, where higher prosthesis index associated with greater prosthesis usage (based on wear frequency and skill) [$r_{(30)}$=0.43, p=0.01]. Together, these findings demonstrate the categorisation hypothesis explains differences in user's prosthesis representation in the OTC, both with respect to controls and inter-individual prosthesis usage.

It is possible that the effects of embodiment are present in a subset of users that rely on their prosthesis for daily function most, but that this effect is masked in the group effect by the wide range of usage in our group of prosthesis users. We therefore further tested the relationship between visual embodiment and prosthesis usage by correlating the Hand-similarity index with a prosthesis usage score, reflecting usage time and habits (see 2.4 Methods). According to the embodiment hypothesis, hand-like prosthesis representation should scale with prosthesis usage. We found no significant correlation between the Hand-similarity index and everyday prosthesis usage (or with tool-similarity; $r_{(30)}$=-0.03, p=0.86), suggesting that prosthesis embodiment is not a strong predictor of usage (Figure 2.3B).

According to the categorisation hypothesis, prosthesis usage should promote a more independent representation of prostheses. This hypothesis predicts that within our multidimensional space, both prosthesis conditions would move away from the existing natural categories (e.g., the distance between cosmetic prostheses and hands will become larger while their distance from tools will become smaller, See Figure 2.3D) and towards one another (smaller distances between cosmetic and active prostheses). In other words, the two different prosthesis types will form a prosthesis cluster within the hand-tool axis. We calculated a Prosthesis-similarity index for each participant (See 2.4 Methods and supplementary Figure S3 for inter-category pairwise distances). We found a significant group difference of the Prosthesis-similarity index ($t_{(54)}$=-2.55, p=0.01; Figure 2.3E). This indicates that using a prosthesis alters one's visual representation of different prostheses types into a distinct category and does so in a way that is more complex than prostheses simply becoming more hand- or tool-like. Although previous studies suggest tool representation is left-lateralised (Bracci et al., 2012; Chao & Martin, 2000), the reported effect was robust across both hemispheres (Right OTC: $t_{(54)}$=-2.25 p=0.03, Left OTC: $t_{(54)}$=-2.66, p=0.01). Exploratory data-driven analysis ran on the one-handers pair-wise distances comprising the Prosthesis-similarity index further revealed that the departure of the active prostheses in particular away from its native 'tool' category is linked with an increased association with cosmetic prostheses (See supplementary Table S4).

Supporting the interpretation that different neural representational structure in prosthesis users is associated with prosthesis usage, we found a significant positive correlation between the Prosthesis-similarity index and the prosthesis usage score described above ($r_{(30)}$=0.43, p=0.01, Figure 2.3F). In other words, the more users use a prosthesis the more they represented the different prostheses types as a separate category. Conversely, individuals who don't use a prosthesis frequently have a more similar representational structure to that of controls.

The two indices for Hand- and Prosthesis-similarity are not statistically independent, and as such we were not able to compare them directly. However, we could use them as a model for predicting daily life prosthesis usage. Comparing the correlation between prosthesis usage and the indices for the two hypotheses (embodiment and categorical) revealed a significant difference (z=-2.52, p=0.01). Therefore, at least when considering unfamiliar prostheses, the Prosthesis-similarity index is a better predictor of prosthesis usage than the Hand-similarity index.

2.2.3 Prosthesis categorisation doesn't depend on users' developmental period of hand loss or prosthesis type

When considering hand-selective neural resources, individuals who were born without a hand might develop different representational structures than those with an acquired amputation (Wesselink et al., 2019). Considering this, we tested whether the Hand-similarity index differed between the two prosthesis-users sub-groups (congenitals versus amputees), and found no significant differences ($t_{(30)}$=-.615, p=0.54). Moreover, the reported Prosthesis-similarity effects prevailed even when accounting for any potential differences between the two sub-groups, as demonstrated by an analysis of covariance (ANCOVA) with sub-group (congenital vs amputees) as a fixed-effect and usage as a covariate. The ANCOVA revealed no significant sub-group effect ($F_{(1,29)}$=2.02, p=0.17) – demonstrating that Prosthesis-similarity does not significantly differ due to cause/developmental period of hand-loss; and a nearly significant usage effect ($F_{(1,29)}$=4.11, p=0.052) – indicating that the relationship between prosthesis categorisation and usage is relatively independent from potential sub-group effects.

Beyond cause of limb-loss, the users tested in this study also diverged with respect to prosthesis type, shape and history of usage, involving primary users of cosmetic (40%), active (41%, comprising of mechanical hook [body-powered; 25%] and myoelectric [motor-powered, 16%]), as well as non-prosthesis users (16%) and a hybrid user (3%; see Table 2.1). A key question is what aspects of the prosthesis itself might affect neural prosthesis adoption in OTC. Since our key focus is on prosthesis usage, we looked at whether individuals who primarily use a prosthesis that has a degree of active grip control (e.g., a mechanical hook) show different effects for those who primarily use a cosmetic prosthesis that affords more limited motor control (no grip). Comparing the Prosthesis-similarity index of users of the two prosthesis types revealed no significant effect ($t_{(20)}$=.055, p=.96). Using an ANCOVA with primary prosthesis type in daily life (cosmetic/active prosthesis) as a fixed-effect and usage as a covariate revealed no prosthesis type effect ($F_{(1,19)}$=.432, p=0.52) – indicating that the categorisation effect might not depend on the type of prosthesis individuals primarily use. The usage effect remained significant ($F_{(1,19)}$=6.01, p=0.02) – indicating that the correlation between usage and categorisation is independent of prosthesis type. Repeating the same analysis with the Hand-similarity index revealed no significant effects – indicating that even when accounting for prosthesis type, no relationship is found with visual embodiment. Though null results should be interpreted with caution, our analysis indicates that the categorisation effect observed in prosthesis users is not driven by the prosthesis design or control mechanism but by the functionality the user extracts from it (as reflected in our daily usage scores).

In the active prosthesis condition, a minority of active prosthesis users (n=5) were shown images of a myoelectric prosthesis (that is not their own; Table 2.1 marked in asterisks). Since these are arguably visually distinct from the mechanical hooks seen by the control participants, we repeated the analysis of Prosthesis-similarity index by replacing the subset of relevant pairwise distances relating to the active prosthesis with the mean distances of the prosthesis users' group (See 2.4 Methods). In this analysis the observed effect remained but was reduced to a trend ($t_{(54)}$= -1.87, p=0.067). Importantly, the correlation between categorisation and usage, remained significant ($r_{(30)}$=0.48, p=0.006) even when excluding the myoelectric users from the analysis altogether ($r_{(25)}$=0.46, p=0.015). This further analysis confirms that our findings were not driven by the subset of myoelectric active prostheses.

2.2.4 Own prosthesis representation

The results discussed so far were derived from visual presentation of prosthesis exemplars that each user was not personally familiar with, allowing us to easily compare the results between the users and controls. However, under the embodiment framework, it could be argued that embodiment can only be achieved for the user's own prosthesis. To account for this possibility, in addition to the general prosthesis types shown to all participants, most prosthesis users (n=26, see 2.4 Methods and Table 2.1) were also shown images of their own prosthesis (for the many prosthesis users using more than one prosthesis, this refers to the prosthesis each user wore on the day of testing). Since controls do not have a prosthesis of their own, in this analysis we compared the user's own prosthesis to the same prosthesis type shown to controls. Therefore, cosmetic 'own' prostheses (n=15) were matched with controls' general cosmetic condition, and active 'own' prostheses (n=11), were matched with the controls' general active condition. To allow us to group values across the cosmetic and active prostheses users, the distances between the 'own' prosthesis from hands and tools were normalised by the mean distances measured from the control group (using the above-mentioned conditions). Since we hypothesized that altered prosthesis representation is driven by usage, the controls' averaged distance is used here as a 'baseline' measure of how the representation is structured before prosthesis use. This normalised score was entered into a one-sample t-test for statistical comparison.

Based on the embodiment hypothesis, users should show greater similarity between users' own prosthesis and hands. Instead, we found that users showed significantly greater dissimilarity (greater distances), relative to controls, indicated by a normalised distance which was greater than 1 [$t_{(25)}$=2.85, p=0.009]. This analysis therefore shows that users' own prostheses are less similar to hands, providing direct evidence against the embodiment hypothesis. The normalised 'own' prosthesis distance from tools was also found to be significantly greater than 1 [$t_{(25)}$=2.91, p=0.008], further supporting the categorisation interpretation. We also repeated the analysis as described above, but this time we standardised distances for 7 users with an 'own' active prosthesis with hand-like visual features (see Table 2.1) with control's cosmetic prosthesis. This complementary analysis produced similar results for hands [$t_{(25)}$=4.33, p<0.001] but not for tools [$t_{(25)}$=1.62, p=0.118] (Figure 2.3C). This means that even when taking both visual-feature and operational considerations, prosthetic limbs are not represented as hands in their owner's visual cortex.

2.2.5 Prosthesis representation beyond EBA

To demonstrate that our results are not specific to our ROI definition in OTC of EBA, we've repeated the same analysis, and found similar results, in 'hand' and 'tool' ROIs within OTC, generated from the meta-analysis tool Neurosynth (Yarkoni et al., 2011) (see supplementary Text S1 and supplementary Figure S4).

We next explored prosthesis representation beyond OTC. The stimuli used in the current study were specifically designed to interrogate the information content underlying prosthesis representation in body-selective regions in the OTC. Nevertheless, as demonstrated in supplementary Figure S5A, the visual stimuli also significantly activated the intraparietal sulcus (IPS), providing us with an opportunity to explore visual prosthesis representation in a dissociated brain area (though notably, this was observed less consistently within individual subjects). Since 11 of the participants did not have enough significantly activated voxels within IPS to meet our ROI criteria, we constructed an anatomical ROI based on the Juliech Histological Atlas in FSL, including human intraparietal (hIP)1-3 bilaterally (Choi et al., 2006; Scheperjans et al., 2008) (see supplementary Figure S5B). With respect to the representational structure, we did not find significant differences between prosthesis users and controls when comparing both the Hand- and Prosthesis-similarity indices, even when wavering corrections for multiple comparisons which are customary for exploratory analysis (Hand-similarity: $t_{(54)}=0.71$, $p=0.48$; Prosthesis-similarity: $t_{(54)}=-0.45$, $p=0.66$). This could be due to insufficient power to explore this representational structure, or possibly due to a different organising principle in this region. However, we did find that users showed significantly greater dissimilarity (greater distances), relative to controls, when comparing the representation of their own prosthesis to that of both hands and tools (hand: $t_{(25)}=10.11$, $p<0.001$; tool: $t_{(25)}=4.62$, $p<0.001$, corrected for 2 comparisons, see supplementary Figure S5C). This analysis indicates that in parietal cortex, similar to the OTC, users' own prostheses are less similar to hands and tools, providing further support against the embodiment hypothesis.

2.3 Discussion

Here we used an fMRI brain decoding technique to probe the information content underlying visual prosthesis representation in the OTC. Previous research shows that prosthesis users are able to activate hand-selective areas in the OTC when viewing a prosthesis (Van Den Heiligenberg et al., 2018). These areas, however, encompass a rich representational structure, spanning well beyond visual hand processing. It is therefore unknown whether by utilising these hand-selective areas, the users' brain actually represents the prosthesis as a hand, or whether it follows a different representational principle. We pitted the embodiment theory against another prominent theory - the categorisation theory – which is well established in visual neuroscience (Reddy & Kanwisher, 2006) (as detailed below), but to our knowledge hasn't been explored for wearable devices. While not directly opposing, both theories generate different predictions on how a prosthesis should be represented in the brain of its user. Contrary to the embodiment theory, we found that prosthesis users represented their own prosthesis unlike a hand. For unfamiliar prostheses, users formed a prosthesis category, distinct from their natural (existing) categories (hands and tools), as demonstrated in controls. Importantly, this shift scales with usage, such that people who use their prosthesis more in daily life show more independence of the prosthesis category. When comparing the two models' success in explaining inter-individual differences between prosthesis users, we find that the prosthesis category model was significantly more correlated with prosthesis usage. This indicates that for visual representation of unfamiliar prostheses, categorisation provides a better conceptual framework than embodiment. Together with preliminary results showing that prosthesis users exhibited a less hand-like representation of their own prosthesis in parietal cortex, our results collectively show that neural visual embodiment does not predict successful adoption of wearable technology by the human brain. Despite benefiting from hand-selective cortical resources (Van Den Heiligenberg et al., 2018), the prosthesis is not ‘embodied’ into people’s visual hand representation. We also did not find any evidence for greater representation of prostheses as tools. However, since the experimental design and analysis we implemented were a priori focused on visual hand representation in OTC, it is possible that other brain areas might find a different representational ‘solution’ to support the daily use of an artificial limb.

As stated above, an intuitive and increasingly popular view that has been inspiring biomedical design and innovation is that embodiment will optimise the usage of technology, such as upper-limb prostheses (Giummarra et al., 2008; Hellman et al., 2015b; Longo et al., 2016; Marasco et al., 2018; Pazzaglia & Molinari, 2016; Rognini et al., 2019; Tyler, 2015; Valle et al., 2018). How can this view be resolved with our findings?

One potential solution originates from the fact that embodiment is a multifaced phenomenon (de Vignemont, 2011), with distinct levels (i.e., phenomenological, cognitive, neural; see Introduction). In a recent study where we probed the phenomenological and cognitive levels of prosthesis embodiment, we found both to correlate with prosthesis usage (Maimon-Mor, Obasi, et al., 2020b). Here, we focused our research on the neural level, since it is entirely unknown whether objective representation of the prosthesis as a body-part associates with prosthesis acceptance and usage, let alone benefits it. It is possible, and even likely, that embodiment manifests differently in each of these distinct levels, which may also vary in their importance or even relevance for successful technological implementation (Makin et al., 2017). To disentangle the complex concept of “embodiment”, future studies should aim to acquire measurements of the different levels of embodiment together with a detailed account of prosthesis skill and use.

A second important consideration is that embodiment is a multisensory process, involving multiple brain areas beyond visual cortex (Ehrsson, 2020; Gentile et al., 2013; Makin et al., 2008). Here we focused on visuomotor processing, and our experimental approach does have some limitations that should be considered. For example, our use of static images was designed to drive activity in the OTC, but not in other sensorimotor-related regions in the parietal and frontal regions (Macdonald et al., 2017), thereby limiting our conclusions to high-level visual cortex. The use of generic hand images that are not the participants' own hands can also be limiting when approaching questions of embodiment. Here it is important to mention that despite using a profoundly non-ecological task in the scanner, the resulting brain representations, as captured with our Prosthesis-similarity index, correlated significantly with the extent of everyday prosthesis usage. Therefore, despite the inherent limitations of our fMRI task, our task outcomes are ecologically relevant. Still, it is possible that other brain areas involved more directly in motor planning would produce other representational structures with respect to hand representation. Future research aimed at this question should take into consideration that at present, commercially available prosthesis motor control is fundamentally different from that of motor control of the hand, producing further potential challenges for sensorimotor embodiment.

Thirdly, and most speculatively, it is possible that the prosthesis may still be represented in OTC as a body part, but one that is not a hand. After all, prosthesis users have strong semantic and sensorimotor knowledge of a hand (all users in the study had one intact hand; acquired amputees had prior experience of their missing hand, including lingering phantom sensations; see also (Striem-Amit et al., 2017) for related findings showing normal visual hand representation in individuals born without both hands). Their experience with operating a prosthesis is fundamentally different from that of a hand. If body representation is not strictly tuned to the specific fine-grained features of a given body part (e.g. the digits of the hand), but is instead also represented at a higher level [e.g. effectors (Hahamy et al., 2017) or based on other functionality features (Graziano & Aflalo, 2007)], then the dissociation of prostheses from hand representation observed in our study should not be taken as evidence for lack of embodiment per se, but rather lack of embodiment as a hand. In this context the previously reported recruitment of hand-specific visual cortical regions, could reflect an underlying embodied representation of a prostheses as a (non-hand) body part. Therefore, we propose that future studies of artificial limb embodiment should not be limited to identifying and/or quantifying hand representation (as the current common practice, e.g., using the rubber hand illusion).

Instead of visual hand embodiment (or tool-like representation), we found that a significant amount of individual differences in prosthesis usage can be predicted by the extent of prosthesis categorisation within the visual body-selective area, providing a significantly better model than hand-embodiment. This result is also consistent with the known organising principle of the OTC, where categorical representation reflects our knowledge of grouping and patterns, which are not necessarily present in the bottom-up sensory inputs (Braunlich et al., 2017; Op de Beeck et al., 2019; Reddy & Kanwisher, 2006; Seger & Miller, 2010). Moreover, categorical representation in OTC was shown to reflect individual differences in conceptual knowledge (Braunlich & Love, 2018). Accordingly, people who acquire a specific visual expertise, such as car experts, show increased activity in object-selective areas in OTC (for a review see Harel, 2016). Research on object-experts, therefore, provides compelling evidence for the role of visual learning and experience in shaping and fine-tuning categorical representation. Although various studies have demonstrated a relation between expertise and activation, few studies performed multivariate analyses, and those that did reported mixed results (Bilalić et al., 2016; Gomez et al., 2019; Martens et al., 2018; McGugin et al., 2015; Ross et al., 2018). For example, Martens and colleagues (2018) found that expertise did not alter the representational configuration of the category of expertise, while McGugin and colleagues (2015) who studied car representation of experts in the Fusiform Face Area, report that car representation became more similar to that of faces with expertise. In this context, our present results provide a novel perspective on visual expertise. This is because our results show divergence of prosthesis representation from the 'natural' categories normally existing in this brain area, consistent with the formation of a new categorical representation. In other words, rather than refining a category, prosthesis usage results in the formation of a new category. Gomez and colleagues (2019) recently reported that childhood experience with playing a Pokémon videogame relates to increased classification of Pokémon, compared with other related categories, in the ventral occipital cortex (Gomez et al., 2019). Extending this finding, we report that categorical prosthesis representation correlates with (ongoing) visuomotor experience in adulthood. As these effects were found in both congenital and acquired one-handers, this prosthesis categorisation effect doesn't seem to relate to a specific developmental period. Since prosthesis usage relies on visuomotor expertise, it is difficult for us to disentangle the relative contribution of perceptual expertise to the observed prosthesis categorisation. Further research examining the representation of prosthesis in exclusively perceptual experts (e.g., prosthetists) will provide an interesting test case for our expertise hypothesis.

A further distinguishing feature of prosthesis users compared to other experts, is that they not only have increased experience with prosthetic limbs but also, arguably, a reduction in exposure to hands, at least from a first-person's perspective. Reorganisation is the process by which a specific brain area qualitatively changes its input-output dynamics to support a novel representation. This raises the question of whether or not the OTC becomes reorganised to support a new visual function (prosthesis control, known to strongly rely on visual feedback (Antfolk et al., 2013; Tan et al., 2014)). In this context, in recent years adaptive behaviour has been suggested (Hahamy et al., 2015, 2017; Makin, Cramer, et al., 2013; Philip & Frey, 2014;

Stoeckel et al., 2009b) and challenged (Striem-Amit et al., 2017, 2018b; Yu et al., 2014) as a causal driver of brain reorganisation. According to this framework, the function of the deprived cortex is not reassigned, instead it is the input (prosthesis versus hand) that changes, while the local processing and resulting output persist (domain specificity; Heimler et al., 2015; Mahon & Caramazza, 2011). For example, in a recent study conducted in individuals with a congenitally missing limb, multiple body parts used to compensate for the missing limb's function benefited from increased activity in the missing hand's sensorimotor cortical area (Hahamy et al., 2017; replicated in Hahamy & Makin, 2019). It was, therefore, suggested that opportunities for reorganisation may be restricted by a pre-determined functional role of a given brain area, e.g., hand resources will only support processing related to hand-substitution behaviours (other body parts or a prosthesis). This framework has been successfully implemented to demonstrate that the categorical organisation of OTC is preserved following congenital blindness (He et al., 2013; Peelen et al., 2013; Striem-Amit et al., 2012). For example, the OTC body area was shown to be selectively activated by tactile (Kitada et al., 2014) and auditory (Striem-Amit & Amedi, 2014) inputs conveying hand/body information. Our findings advance beyond these studies by demonstrating that a parallel form of reorganisation can occur even when the relevant sensory pathway (vision) is largely unaffected, further highlighting the role of daily behaviour in shaping brain organisation across the lifespan.

Finally, our results suggest that the relationship between prosthesis representation and usage is independent of key design and usage features of the artificial device (such as visual mimicry of the human hand) and cause of limb loss (congenital or acquired). This should inspire future efforts in neurologically-informed substitution and augmentative artificial limb design to not be strictly confined to biomimetics, a design principle that is currently highlighted in the development of substitution technology (Bensmaia & Miller, 2014; for example, the vine prosthesis; de Oliveira Barata et al., 2017).

To conclude, we provide a novel neural correlate for the adoption of wearable technology that is distinct from visual embodiment of a prosthesis as a hand. Successful prosthesis usage, in terms of both wear-time and habit in daily life, was predicted not by visual embodiment (hand-similarity) or tool-similarity, but by a more distinct categorical representation of artificial limbs. Understanding whether the brain can treat a prosthesis as a hand, and whether this hand-like representation provides a real advantage for prosthesis users, will have important implications on future design and assessment of wearable technology. Considering the limitations related to our focus on visual prosthesis representation in passive settings we are currently unable to offer a sweeping answer to how the entire brain represents artificial limbs. However, our findings provide an important alternative to the highly prominent embodiment theory that needs to be considered. As such, much more research is necessary to provide a comprehensive understanding of the neural basis of successful prosthesis usage in the human brain.

2.4 Methods

2.4.1 Participants

Thirty-two individuals missing an upper limb [one-handed prosthesis users, *mean-age(SD*) = 42.3(11.8), 12 females, 8 missing their right hand] were recruited to take part in the study (Table 2.1). Sixteen prosthesis-users lost their hand following an amputation and 16 had a unilateral congenital upper-limb below-elbow deficiency (due to complete arrest of hand development). One additional prosthesis user was recruited to the study but did not participate in the scanning session due to claustrophobia. In addition, 24 age- and gender-matched two-handed controls (*age* = 41.7(13.1); 12 females; 8 left-handed) took part in the study. Fourteen of the control participants were family members, friends or held professional relationships with prosthesis users, resulting in passive visual experience of prosthesis usage. All participants took part in a larger study, involving multiple tasks (https://osf.io/kd2yh/). Univariate data from the fMRI task reported here was previously published (Van Den Heiligenberg et al., 2018). This study was approved by the Oxford University's Medical Sciences inter-divisional research ethics committee (Ref: MSD-IDREC- C2-2014-003). Written informed consent and consent to publish was obtained in accordance with ethical standards set out by the Declaration of Helsinki.

2.4.2 Prosthesis usage measurements

Prosthesis usage was assessed by combining two, highly correlated, measurements of usage: prosthesis wear frequency and a Prosthesis Activity Log (PAL) (van den Heiligenberg et al., 2017; Van Den Heiligenberg et al., 2018). Participants rated their prosthesis wear frequency on a scale: 0-never, 1-rarely, 2-occasionally, 3-daily (<4 hours), 4-daily (4-8 hours), 5-daily (>8 hours). Some participants use more than one type of prosthesis, in that case the measurement from the most frequently used prosthesis was used. The PAL is a revised version of the Motor Activity Log (MAL) (Uswatte et al., 2006) as described in (Makin, Cramer, et al., 2013). In brief, participants were requested to rate how frequently (0-never, 1-sometimes, 2-always) they incorporate their prosthesis in an inventory of 27 daily activities, with varying degrees of motor control. PAL is calculated as the sum of the levels of frequencies in all activities divided by the maximum possible sum (27x2) creating a scale of 0 to 1. This questionnaire, indexing bimanual usage, was previously validated using limb acceleration data (Makin, Cramer, et al., 2013) and behavioural lab testing (Hahamy et al., 2017), collected in ecological settings. As neither measure is able to fully capture prosthesis use, both the prosthesis wear-frequency and PAL were Z-transform and summed to create a prosthesis usage score.

2.4.3 Stimuli

Participants viewed still object images of the following categories: (i) hands (upper limbs with and without the arm, in multiple orientations and configurations, and of different sizes, genders, and skin-colors; hereafter hands); (ii) man-made hand-held tools; (iii) cosmetic prostheses (aesthetically hand-like, but non-operable), (iv) active prostheses (affording a grip; either mechanical hooks and myoelectric prostheses); and, (v) (when available) participants' own prosthesis (more details below). For hands and prosthesis images, the effector was matched to the prosthesis-users' missing-hand side or the non-dominant hand in controls (e.g., participants missing their left hand were presented with 'left-handed' hands/prostheses). Headless bodies and typically non-manipulable man-made object images were also included for localising independent ROIs (see *Region of interest* section). Additional conditions which were also included in the fMRI paradigm and initial analysis but not reported here were: dismorphed images (originally intended to account for low-level visual activity but discarded after univariate analysis revealed increased activity in OTC), and lower limbs (intended as a control body part but not included in final analysis).

Images used for the main stimulus categories can be found at (https://osf.io/kd2yh/). All images had their background removed, normalized for size, placed on an equiluminant grey background and overlaid with a red fixation square. Non-prosthesis conditions were taken from an online database and involved multiple exemplars, whereas each of the three prosthesis conditions involved multiple shots of a single prosthesis of different orientations. We chose to use multiple configurations of hands and prostheses to probe the experience of congenital one-handers and control participants (who mostly see prostheses/hands-of-the-missing-side from a

3rd person perspective, respectively). We note that previous studies probing visual hand representation in similar populations (van den Heiligenberg et al., 2017), including specifically in OTC (Striem-Amit et al., 2017) used a similar approach. We further note that the few studies finding differences between egocentric/allocentric (Saxe et al., 2006) or self/others (Myers & Sowden, 2008) visual hand representation in OTC identified lateralised effects to the right OTC, whereas our effects are comparable across hemispheres. Prosthesis images of other users' prostheses (in the cosmetic and active conditions) or of the participant's prosthesis (in the 'own' condition) were taken by the experimenters prior to the functional MRI session. The subset of the active prosthesis users (Marked with an asterisk in Table 2.1) were shown another myoelectric prosthesis in the active prosthesis condition.

In the 'own' prosthesis condition, all prosthesis-users who had brought their prosthesis to the study were presented with images of their own prostheses, either cosmetic or active (n=26, see Table 2.1). All other participants (i.e., the remaining six prosthesis-users who did not bring a prosthesis and all control participants) were shown pictures of their own shoe instead. Shoes were selected as a familiar external object that was intended to exert similar cognitive effects (e.g., in terms of arousal) as the prosthesis, and therefore minimize differences in the scan time course across groups. Since we had no a priori interest in studying shoe representation, the shoe condition was not included in further analysis.

Post-hoc shape similarity analysis (Belongie et al., 2002) confirmed that the prosthesis images spanned a diverse range, resulting in similar shape dissimilarity for the two prosthesis types with respect to hand and tool exemplars (supplementary Figure S2). It is highly likely that other measurements of visual similarity (e.g., based on contrast/colour comparison, or perceptual judgements) would reveal more distinct inter-categorical (dis)similarities. However, any such visual (dis)similarities should impact inter-categorical representational similarity in the control group. As such, in the present study all key analyses are interpreted with respect to the controls, providing us with a representational ‘baseline’.

2.4.4 Experimental design

Each condition consisted of 8 different images. In each trial a single image from one of the conditions was shown for 1.5s, followed by 2.5 s of fixation. Participants were engaged in a one-back task and were asked to report whenever an image was repeated twice in succession. This occurred once for each condition within each functional run, resulting in 9 trials per condition per run (8 distinct exemplars and one repetition). This design was repeated in 4 separate functional runs, resulting in 36 events per condition. First-order counterbalancing of the image sequences was performed using Optseq (http://surfer.nmr.mgh.harvard.edu/optseq), which returns the most optimal image presentation schedule. Run order was varied across participants. The specifics of this design were validated against an event-related design with a jittered interstimulus interval and a block design during piloting (n= 4). Stimuli were presented on a screen located at the rear end of the scanner and were viewed through a mirror mounted on the head coil. Stimulus presentation was controlled by a MacBook-Pro running the Psychophysics Toolbox in MATLAB (The MathWorks, Natick, MA).

2.4.5 MRI data acquisition

The MRI measurements were obtained using a 3-Tesla Verio scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. Anatomical data were acquired using a T1-weighted magnetization prepared rapid acquisition gradient echo sequence with the parameters: TR=2040ms, TE=4.7ms, flip angle=8° and voxel size=1mm isotropic resolution. Functional data based on the blood oxygenation level-dependent signal were acquired using a multiband gradient echo-planar T2*-weighted pulse sequence (Uğurbil et al., 2013) with the parameters: TR=1300ms, TE=40ms, flip angle=66°, multiband-factor=6, voxel-size=2mm isotropic and imaging matrix=106x106. Seventy-Two slices with slice thickness of 2mm and no gap were oriented in the oblique axial plane, covering the whole cortex, with partial coverage of the cerebellum. The first dummy volume of each scan was saved and later used as a reference for coregistration. Additional dummy volumes were acquired and discarded before the start of each scan to reach equilibrium. Each functional run consisted of 256 volumes.

2.4.6 Pre-processing and first-level analysis

Functional MRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration of the functional data to the high resolution structural image was carried out using the boundary based registration algorithm (Greve & Fischl, 2009). Registration of the high resolution structural to standard space images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001) and was then further refined using FNIRT nonlinear registration (Andersson et al., 2007b, 2007a). The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); B0-unwarping using a separately acquired field-map; spatial smoothing using a Gaussian kernel of FWHM 4mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). The time series model included trial onsets and button presses convolved with a double gamma HRF function, six motion parameters were added as confound regressors. Indicator functions were added to model out single volumes identified to have excessive motion (>1mm). A separate regressor was used for each high motion volume, no more than 9 volumes were found for an individual run (3.5% of the entire run).

2.4.7 Occipitotemporal Region of Interest (ROI)

Since the focus of the study was on visual representation of prostheses in the occipitotemporal cortex, the representational similarity analysis was restricted to individualised ROIs. ROI of the extrastriate body area (Downing et al., 2001) were identified bilaterally in each participant, by selecting the top 250 activated voxels, in each hemisphere, in the headless-bodies > non-manipulable objects. Voxel selection was restricted to the lateral occipital cortex, inferior and middle temporal gyri, occipital fusiform gyrus, and temporal occipital fusiform cortex (all bilateral), as defined by the Harvard-Oxford atlas (Desikan et al., 2006). Voxels from both hemispheres were treated as a single ROI (See supplementary Table S3 for all analyses repeated for each hemisphere separately). Mean activity within the ROI for each participant was calculated by averaging the parameter estimate (beta) for each condition across all 500 voxels.

2.4.8 Representational Similarity Analysis

To assess the hand-prosthesis-tool representation structure within the ROI, pairwise distances between conditions were calculated using a multivariate approach, generally known as Representational Similarity Analysis (Diedrichsen & Kriegeskorte, 2017). Prior to performing the multivariate analysis, we first examined differences in univariate activity in the ROI, which could drive differences in the multivariate analysis. When comparing activity levels (averaged across all voxels) between controls and prosthesis-users within this region, no significant differences were found for each of the image conditions of hands, tools and prostheses ($p>0.1$ for all, see supplementary Table S2), indicating that the two groups did not activate this region significantly differently. We then continued with the multivariate analysis. For each participant, parameter estimates of the different conditions and GLM residuals of all voxels within the ROI were extracted from each run's first-level analysis. To increase the reliability of the distance estimates, parameter estimates underwent multi-dimensional normalisation based on the voxels' covariance matrix calculated from the GLM residuals. This was done to ensure that parameter estimates from noisier voxels will be down-weighted (Walther et al., 2016). Cross validated (leave-run-out) Mahalanobis distances (also known as *LDC* - linear discriminant contrast) (Nili et al., 2014; Walther et al., 2016) were then calculated between each pair of conditions. Analysis was run on an adapted version of the RSA Toolbox in MATLAB (Nili et al., 2014), customised for FSL (Wesselink & Maimon-Mor, 2018). Visualisation of the distances in dendrogram was perform using the plotting functions available in the RSA Toolbox.

2.4.9 Hand-Similarity and Prosthesis-Similarity Indices

Two indices were calculated to test each of the aforementioned predictions - one based on embodiment and the other on the categorical structure of OTC. Each index's formula was designed so that positive values support the prediction. Therefore, similar to GLM contrasts, each of the relevant pairwise distances were weighed with a positive multiplier if, under the specific prediction, that distance should grow (decreased similarity) in prosthesis-users, and a negative multiplier if it should shrink (greater similarity). For instance, the embodiment hypothesis predicts that for both prostheses (active and cosmetic) the distance from tools would grow (will be less similar), while the distance from hands will shrink (will be more similar). Therefore, the formula used to calculate the Hand-Similarity index was: (Tools↔CosmP + Tools↔ActP) – (Hands↔CosmP + Hands↔ActP), where ↔ indicates the distance between a pair of conditions. Using the same logic, the Prosthesis-similarity index was calculated as a measurement of how much the two prosthesis conditions are represented as a separate cluster away from their native condition (cosmetic prostheses resembling hands and active prostheses resembling tools). The index was calculated using the following formula: 3(Hands↔CosmP +

Tools↔ActP) –2(Hands↔ActP + Tools↔CosmP + ActP↔CosmP), see Figure 2.3D for a visualisation of the formula. To control for individual differences in absolute distance values both indices were standardised by the individuals' distances between hands and tools (i.e., the residuals after accounting for the variance in the Hands↔Tools distance; See supplementary Table S3 for all analyses performed with the raw index values).

As mentioned earlier (See 2.4.3 Stimuli), five active prosthesis users viewed images of myoelectric prostheses as the active prosthesis condition while all other participants viewed mechanical hooks under that condition. Since this creates a possible bias in our analysis, we have attempted to remedy this in two ways. The first is to replace all distances that involved the active prosthesis condition with the mean distances of the rest of the users' group. In other words, before calculating the indices, replacing the distances (Tools↔ActP, Hands↔ActP, ActP↔CosmP) for these five individuals with the mean distances of the remaining 27 users. Another approach was to remove these individuals from the analysis altogether.

2.4.10 Analysis by Prosthesis Type

To test the influence of prosthesis type on users' Prosthesis-similarity index, we repeated the same analysis as described above, and compared the Hand- and Prosthesis-similarity indices between individuals using a cosmetic prosthesis (n=13) and active prosthesis users (n=9). The following participants have been excluded from this analysis: (1) Five individuals not using a prosthesis (usage time of 0=never); (2) The five participants that viewed myoelectric prostheses as the active prosthesis condition mentioned above.

2.4.11 Own prosthesis representation

In this analysis we aimed to assess each user's own prosthesis representation, defined by its distance from hands and tools. Our approach was designed to overcome two challenges: First, controls do not have an ‘own’ prosthesis and second, the visual and operational features of different prostheses may vary significantly and need to be accounted for before similarity measures can be averaged across all prosthesis users. Therefore, for each participant, we normalised (divided) the ‘own’ prosthesis distance by the mean distance of a similarly-looking/operating prosthesis, as found in controls. This produced a measure that reflects the magnitude of the representational shift of individual’s ‘own’ prosthesis from the average distance of the control participants. A value of one would therefore indicate no difference between controls and the user’s representation of their own prosthesis. For the seven prostheses users wearing an active prosthesis that had hand-like visual features (See Table 2.1 for a full breakdown of prostheses types), we repeated the analysis twice over, standardising their distances with control’s active and cosmetic prosthesis distances. This allowed us to account for both visual and operational features.

2.4.12 Intra-Parietal Sulcus (IPS) Region of Interest

The IPS region of interest was generated using the Juliech Histological Atlas, including all voxels that have more than 30% probability of being within the grey matter of the intra-parietal sulcus areas: hIP1, hIP2, and hIP3, (Choi et al., 2006; Scheperjans et al., 2008) in both hemispheres.

2.4.13 Statistical analysis

All statistical testing was performed using SPSS (v24), with the exception of the Bayesian analysis which was run on JASP (Jasp Team, 2020). Comparisons between prosthesis-users and two-handed controls were performed using a two-tailed Student’s t-tests. To test the relationship between the indices and individuals’ prosthesis use, a usage score, described above, was correlated with the indices using a two-tailed Pearson correlation. An analysis of covariance (ANCOVA) with prosthesis usage as a covariate was used to test the contribution of several factors such as cause of limb-loss and type of prosthesis used. Own prosthesis analyses were performed using a one-sample t-test, comparing the mean to one as the controls means were used to calculate the individual indices. To interpret key null results, we ran a one-tailed t-test. The Cauchy prior width was set at 0.707 (default). We interpreted the test based on the well accepted criterion of Bayes factor smaller than 1/3 (Dienes, 2014; Wetzels et al., 2011) as supporting the null hypothesis. Corrections for multiple comparisons were included for exploratory analysis when resulting in significant differences, as indicated in the results section. To minimise flexible analysis which could lead to p-hacking (Makin & Orban de Xivry, 2019), only a limited set of factors, pre-specified in the initial stages of the analysis or based on the reviewer's comments, were tested in this manuscript. Further exploratory analysis on other recorded clinical factors can be conducted using the full demographic details: https://osf.io/kd2yh/ .

Chapter 3 | Early life experience sets hard limits on motor learning as evidenced from prosthetic arm use

Adapted from:

Maimon-Mor, R. O., Schone, H. R., Slater, D. H., Faisal, A. A., & Makin, T. R. (2021). Early life experience sets hard limits on motor learning as evidenced from artificial arm use. bioRxiv.

Chapter Abstract

The study of prosthetic arms provides a unique opportunity to address long-standing questions on sensorimotor plasticity and development. Learning to use a prosthetic arm arguably depends on fundamental building blocks of body representation and would therefore be impacted by early-life experience. We tested prosthetic arm motor-control in two adult populations with upper-limb deficiency: congenital one-handers – who were born with a partial arm and acquired amputees – who lost their biological arm in adulthood. Brain plasticity research teaches us that the earlier we train to acquire new skills (or use a new technology) the better we benefit from this practice as adults. Instead, we found that although congenital one-handers started using a prosthetic arm as toddlers, they produced increased error noise and directional errors when reaching to visual targets, relative to amputees who performed similarly to controls. However, the earlier a congenital one-hander was fitted with a prosthetic arm the better their motor control was. We suggest that visuomotor integration, underlying the observed deficits, is highly dependent on either biological or prosthetic arm experience at a very young age. Subsequently, opportunities for sensorimotor plasticity become more limited.

3.1 Introduction

We move our hands with such apparent ease, yet the underlying process involves complex computations, representations and integration of information across multiple systems and modalities (Scott, 2004; Wolpert, 1997). Learning to move our limbs precisely and accurately begins *in utero*, where embryos have been documented refining arm-to-mouth reaching movements (Zoia et al., 2007). The trajectory of optimising reaching across infancy (Berthier & Keen, 2006; Leed et al., 2019) and childhood (Contreras-Vidal, 2006; Schneiberg et al., 2002; Simon-Martinez et al., 2018; Sveistrup et al., 2008) is highly protracted, roughly plateauing at around 10-12 years of age. In the present study, we investigated reaching behaviour in two groups of individuals who experienced a vastly different motor development but share current motor constraints: congenital one-handers born with a partial upper-limb and acquired amputees who were born with a fully developed upper-limb but lost it as adults. We asked how a sensorimotor system that developed with (amputees) or without (congenitals) experience of a complete arm supports the control of an upper-limb substitute (prosthetic arm). Prosthetic arm motor control provides a unique opportunity to address key questions surrounding sensorimotor plasticity. The flexibility needed to support this new body part is arguably different from that observed in traditional motor learning paradigms (e.g., involving tools) as it might relate to more fundamental building blocks of body representation and the internal models for motor control.

We consider three possible predictions, involving differences in prosthetic arm motor control across these two groups: first, perhaps the most straightforward prediction is that congenitals one-handers' prosthetic arm motor control would be superior to that of amputees. It is often thought that the brain is more plastic during earlier stages of development (Knudsen, 2004). Therefore, it becomes more difficult to acquire radically new motor skills in adulthood, which is probably why most virtuoso musicians and athletes started practicing their trade in their childhood (Penhune, 2011). As mentioned above, congenital one-handers start using prosthetic arms at a very young age (in our sample as early as 3 months with an average of ~2.5 years), even before early training for musical and athletic skills. It therefore stands to reason that in comparison to amputees, who only begin to learn to use their prosthetic arm as adults (in our sample at a mean age of 32), congenital one-handers should have had more time and practice in early childhood to perfect their prosthetic arm motor skill. Moreover, amputees often experience a 'phantom hand' (Stankevicius et al., 2020), rooted in a maintained representation of their missing arm (Bruurmijn et al., 2017; Kikkert et al., 2016; Wesselink et al., 2019) which might in theory interfere with the acquisition of a representation of an arm substitute (the prosthetic arm). Perhaps most importantly, relative to amputees, congenital one-handers tend to make better use of their prosthetic arm in daily life (Biddiss & Chau, 2007a). Together, these considerations lead to a strong hypothesis that congenital one-handers would have had better opportunities for developing sensorimotor prosthetic arm control.

A second alternative hypothesis is that congenital one-handers' early-life disability might offset motor development, but that such disability-related impairment would not necessarily lead to inferior motor performance with a prosthetic arm. In other words, that the performance in the congenital group would be equivalent to that of the acquired group. It could be argued that regardless of the undisputed role of early life experience in shaping brain organisation and function, the canonical brain infrastructure will still exist and be able to support the dormant function, even in congenital one-handers. In the visual domain, children born with high density cataracts who received corrective surgery later in life have been shown to retain some rudimentary forms of visual perception (Gandhi et al., 2017). This hypothesis is consistent with recent studies emphasising normal visuomotor processes and representations of hands of individuals born with no hands (Vannuscorps & Caramazza, 2015, 2016 though see Chapter 1; Maimon-Mor, Schone, et al., 2020; Philip et al., 2015; Philip & Frey, 2011; Wesselink et al., 2019). Moreover, considering these individuals potentially have a lifetime of daily experience controlling a prosthetic arm, it is possible that they will be able to ‘close the gap’ that had started in early development, relative to their able-bodied peers. Indeed, it has been consistently shown how well adults can adapt their motor behaviour to overcome a myriad of perturbations, and learn to perform intricate and skilful tasks (Wolpert et al., 2011).

A third hypothesis asserts that experience with a complete arm early in life might be crucial for the successful integration of any arm, including a prosthetic one. Therefore, motor control of a prosthetic arm would be superior in acquired amputees who had ‘typical’ motor development for their missing arm, relative to congenital one-handers who had atypical motor development. This idea is rooted in the old debate of the relative contributions of nature vs. nurture. Current views consider neural development an interaction between predetermined maturation based on a genetic template and experience (Adolph & Franchak, 2017; Karmiloff-Smith, 1998; Krubitzer & Prescott, 2018). The neural topographical organisation of sensory input across the cortex has been shown to be in part determined by genetics (Miyashita-Lin et al., 1999; Rubenstein et al., 1999). However, for both the motor system and the visual system (an integral input to the sensorimotor loop), early deprivation has been shown to have a permanent effect on development (de Heering et al., 2016; Walton et al., 1992). As such, individuals who, prior to their amputation, benefited from a typical developmental trajectory might be able to rely on the existing upper-limb infrastructure, after amputation, when learning to control a prosthetic arm. This is in stark contrast to congenital one-handers, who never developed an upper limb, due to a developmental malformation, and therefore lack both visual and motor experience of their missing limb during the formative years of their motor development. Based on this hypothesis, amputees would have superior motor control of prosthetic arms, compared to congenital one-handers.

Consistent with this final hypothesis we found that although they had started training to use a prosthetic arm earlier in life, and sustained more elapsed years of prosthetic arm use, congenital one-handers were unable to refine their reaching control to normal levels. Congenital one-handers produced larger reaching errors with their prosthetic arms compared to both prosthetic arm reaches of amputees and non-dominant hand reaches of age-matched controls. We used numerous measures and tasks to interrogate the potential contributors to sensorimotor performance across groups, allowing us to disentangle the different components that might have contributed the aforementioned group differences. Lastly, we explored how the key components contributing to reduced motor control relate to early life experience with a prosthetic arm. Our results suggest that the formation of an arm representation in early life has a long-lasting effect on the incorporation of a prosthetic arm, highlighting that opportunities for sensorimotor plasticity become more limited with age, even across early childhood.

3.2 Results

3.2.1 Congenital one-handers show inferior prosthetic arm motor control

In order to assess motor control of prosthetic arms, participants performed visually guided reaches to a set of targets using a robotic manipulandum device (see Figure 3.1A&B). Motor control measures were compared across three groups: congenital one-handers (*n*=18), amputees (*n*=14) and age-matched controls (*n*=19). All included participants were able to control the robotic handle and perform the task using the same speed-accuracy trade-off parameters following Fitts' Law (see Supplementary Results). Reaching performance was evaluated by measuring the mean absolute error participants made across all targets (see Figure 3.1C). The absolute error refers to the distance from the cursor's position at the end of the reach (endpoint) to the centre of the target in each trial. Participants completed the same task using their intact arm as well, allowing us to control for individual differences relating to aspects of the task that are not prosthetic arm specific. We found no significant group effect ($F_{(2,48)}$=1.05, p=-.14) when comparing the absolute-errors of the intact arm and dominant arm across the three groups (controls, amputees and congenitals). However, this result was inconclusive (BF_{10}=0.65), i.e., supports neither the null nor the alternative hypothesis. We therefore included the intact arm as a confound regressor in subsequent analyses (see result section 6 for additional results and discussion regarding intact arm performance).

We performed an analysis of covariance (ANCOVA) on participants' prosthetic arm errors where participants' intact arm errors were defined as a covariate, and group as a between-subjects variable. We found a significant effect of intact-hand performance ($F_{(1,47)}$=28.65, p<0.001, η_p^2=0.38), i.e., participants who had small errors with their intact arm also tended to have smaller errors with their non-dominant/prosthetic arm. We found a significant group effect ($F_{(2,47)}$=13.81, p<0.001, η_p^2=0.37), indicating the groups differed in their visuomotor performance with their prosthetic arm (or non-dominant arm in controls). Post-hoc comparisons revealed that congenital one-handers exhibited larger errors with their prosthetic arm compared to both the prosthetic arm of amputees (t=-3.77, p_{tukey}=0.001, *Cohen's-d* =-1.39), and the non-dominant arm of controls (t=-5.06, p_{tukey}<0.001, *Cohen's-d* =-1.705). Conversely, amputees' prosthetic-limb errors did not differ from those of controls' non-dominant arm (t=-0.885, p_{tukey}=0.65), indicating a specific deficit in error reaching for congenital one-handers' prosthetic arm. To further explore the non-significant performance difference between amputees and controls, we used a Bayesian approach (Rouder et al., 2009), inputting the smaller effect size of the two reported here (1.39) as the Cauchy prior width. The resulting Bayesian Factor (BF_{10}=0.28) provided moderate support to the null hypothesis (i.e., smaller than 0.33). To summarise, congenital one-handers show significantly inferior prosthetic arm reaching accuracy in our task compared to the other groups (see Supplementary Table S1 for results of the statistical analyses confirming that this effect was not driven by the side (L/R) of the prosthetic arm/non-dominant side).

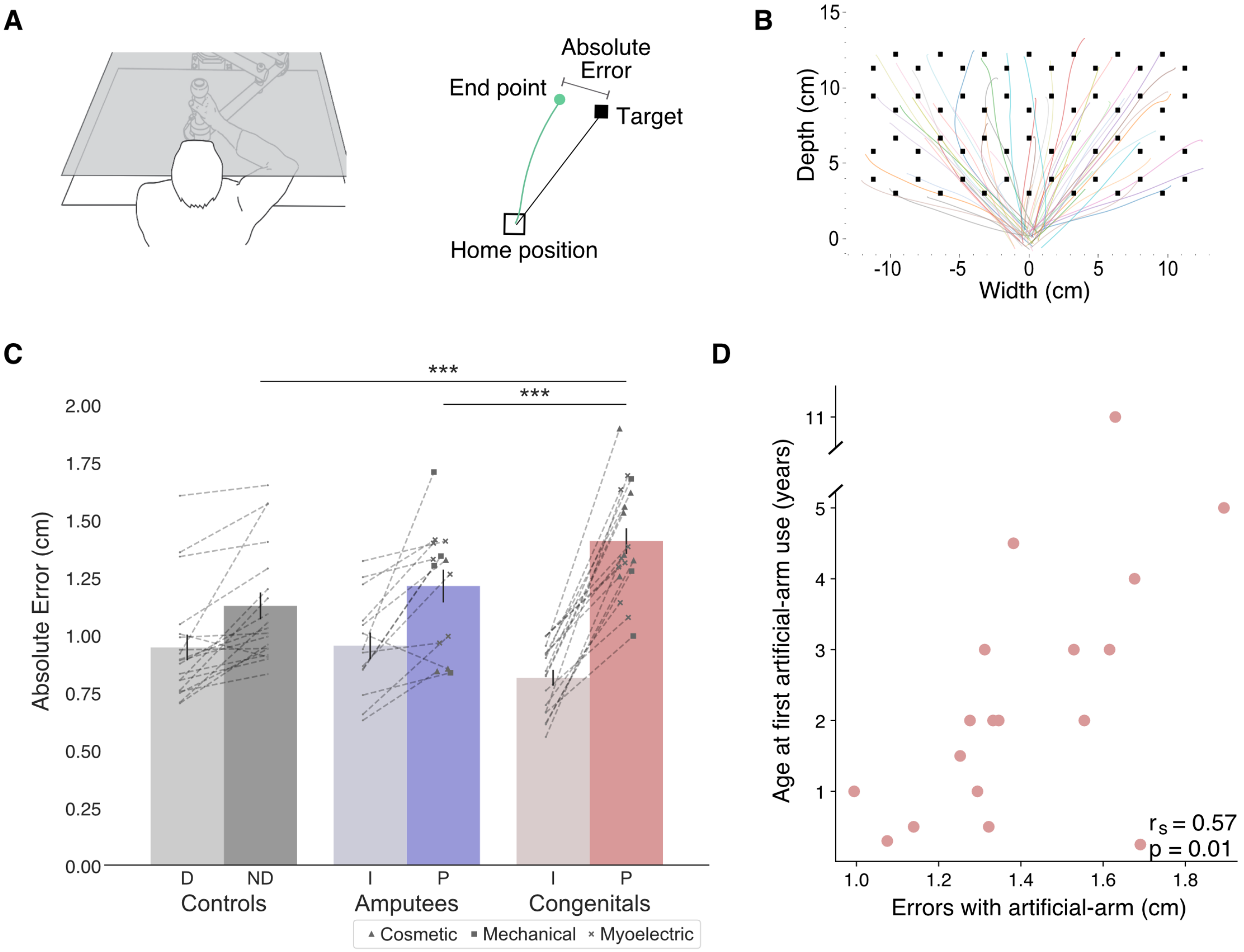


Figure 3.1. *Experimental design and main analyses.* (A) Left: An illustration of the robotic manipulandum device setup. Participants performed reaching movements while holding a robotic handle. A monitor displaying the task components was viewed via a mirror, such that participants did not have direct vision of their arm. Visual feedback was provided as a cursor depicting the current location of the arm. Right: A visualisation of a single trial and the different terms used. In each trial, participants reached from the home position to a single visual target. The green line represents the participant's arm trajectory. (B) Reaching trajectories to all targets from a randomly selected participant. The different coloured lines are trajectories of individual reaching trials. (C) Reaching performance as measured by absolute errors for each group for each arm. Grey, blue and red colours represent controls, amputees and congenitals respectively. Lighter colours represent intact/dominant-arm performance; darker colours represent prosthetic/nondominant-arms. We found a significant group effect ($F_{(2,47)}$=13.81, p<0.001, η_p^2=0.37), with congenital one-handers making larger errors with their

prosthetic arm compared to both amputees' prosthetic arm (t=-3.77, p_{tukey}=0.001, Cohen's-d =-1.39), and controls' non-dominant arm (t=-5.06, p_{tukey}<0.001, *Cohen's-d* =-1.705). Dotted lines connect errors between arms of individual participants. Prosthetic arm markers represent prosthetic arm type. (D) Relationship between age at first prosthetic arm use and prosthetic arm reaching errors in congenital one-handers. Illustration in Figure 3.1A was reproduced from Figure 1A, Wilson, Wong, & Gribble 2010, PLoS ONE, published under the Creative Commons Attribution 4.0 International Public License (CC BY 4.0; https://creativecommons.org/licenses/by/4.0/). D – Dominant arm, ND – Nondominant arm, I – Intact arm, P – Prosthetic arm. *** $p < .001$

3.2.2 Physical aspects of prosthetic arm use do not correlate with endpoint errors

We first wanted to rule out the influence of two crucial physical aspects of prosthetic-limb use: residual-limb length and device type. The length of the residual-limb, used to carry and control the prosthetic arm, can have a potential impact on the level of its motor control. The shorter the residual limb, the more restrictive the prosthetic-limb control is, e.g., due to more restrictive motion and less leverage. Across both amputee and congenital groups, the correlation between absolute reaching error and either residual-limb length was not significant (r_s(30)=-0.23, p=0.2). Moreover, repeating the previously reported ANCOVA analysis while adding residual limb length as a covariate revealed no significant effect of residual-limb length (p>0.2) and, importantly, did not abolish the group effect (p=0.03; for a full statistical report see Supplementary Table S2). Therefore, the length of the residual limb does not play a significant role in the observed group effect for end-point accuracy of prosthetic arm reaches.

It is important to note that while prosthetic arm devices have different levels of wrist- and grasp- control, they are all used similarly during reaching (i.e., in the current task the participants did not use any of the devices additional control features). Yet, we wished to confirm that differences in prosthetic arm types used across the two groups did not affect our findings. The devices used by our participants can generally be categorised into three device-types: (1) 'cosmetic' devices that look like a hand (n=10), these are static devices that do not afford additional control, (2) ‘body-powered’ devices in the shape of a hook (n=7), these include a mechanical grip control, (3) ‘myoelectric’ devices (n=15), these are relatively heavy devices, controlled using signals from the muscles of the residual-limb and powered by motors to perform grip functions (see marker type in Figure 3.1C). Despite the differences in appearance and control mechanisms between devices, the type of device used does not seem to influence endpoint reaching error in our task, as demonstrated by a one-way ANOVA with device type as a between subject variable showing no significant differences between devices ($F_{(2,29)}$=0.435, p=0.65, BF_{10}=0.275).

3.2.3 Congenital one-handers’ prosthetic arm errors originate from increased motor noise

In our analyses so far, we reported the absolute error – the average distance of the endpoint from the visual target across all reaches. An increase in absolute error can be the result of two different type of error components (see Figure 3.2A): bias (e.g., consistently reaching to the left of the target) and noise (variability/spread of endpoints). These are often also referred to as accuracy and precision, respectively. A larger bias is caused by a model-mismatch, for example, an inaccurate internal forward model that produces a biased control policy that consistently fails to accurately transport the arm to the correct location, resulting in poor accuracy. Several different sources can cause a noisier performance, for example: large uncertainties in the sensory estimates of proprioception (Gordon et al., 1995), motor noise (Faisal et al., 2008), or a result of a failed computation (Contreras-Vidal, 2006), e.g. to optimally use sensory inputs to reduce this inherent noise. Assessing these error components separately can give us an insight into the underlying processes that are affected in congenital one-handers.

In order to calculate these measures across all targets, we drew the error vector for each trial (the line connecting the target with the end-point location) and overlaid all the error vectors, as if they were made to a single target. While error vectors are known to be location-dependent (Van Beers et al., 1999, 2004), because we compare bias and noise measures across groups, and the distribution of error vector directions did not differ between groups (Watson-Williams circular test: $F_{(2,48)}=1.95$, $p=0.15$; see Figure 3.2A), these measures are suitable for present purposes. We compared prosthetic arm and nondominant arm biases (distance from the centre of the endpoint to the target) across groups, using intact arm biases as a covariate. The ANCOVA resulted in no significant group differences ($F_{(2,47)}=2.40$, $p=0.1$, $BF_{Incl}=0.72$; see Figure 3.2A). When comparing prosthetic arm and nondominant arm motor noise (spatial standard deviation (SD) of end-points relative to the centre of the endpoints), using intact-hand noise as a covariate, we found a significant group effect ($F_{(2,47)}=14.15$, $p<0.001$, $\eta_p^2=0.38$; see Figure 3.2A). Reflecting the absolute error findings, congenital one-handers exhibited larger motor noise with their prosthetic arm compared to the prosthetic arm of amputees ($t=-2.90$, $p_{tukey}=0.015$, $Cohen's\text{-}d=-0.855$), and the non-dominant arm of controls ($t=-5.31$, $p_{tukey}<0.001$, $Cohen's\text{-}d=-1.65$). Comparing motor noise between amputees' prosthetic arm and controls' non-dominant arm was inconclusive ($t=-2.1$, $p_{tukey}=0.1$, $BF_{10}=1.2$). Similar results were obtained when testing for the unique effect of noise beyond bias, by adding prosthetic arm bias as a covariate when comparing the motor noise of the prosthetic arm errors between the three groups (See Supplementary Table S3 for a full statistical report). These results show that congenital one-handers' prosthetic arm reaches are best characterised by increased noise (end-point variability). In the next analyses, we will test two potential sources of noise: prosthetic arm sense of localisation (proprioception) and adequacy of motor planning and its execution.

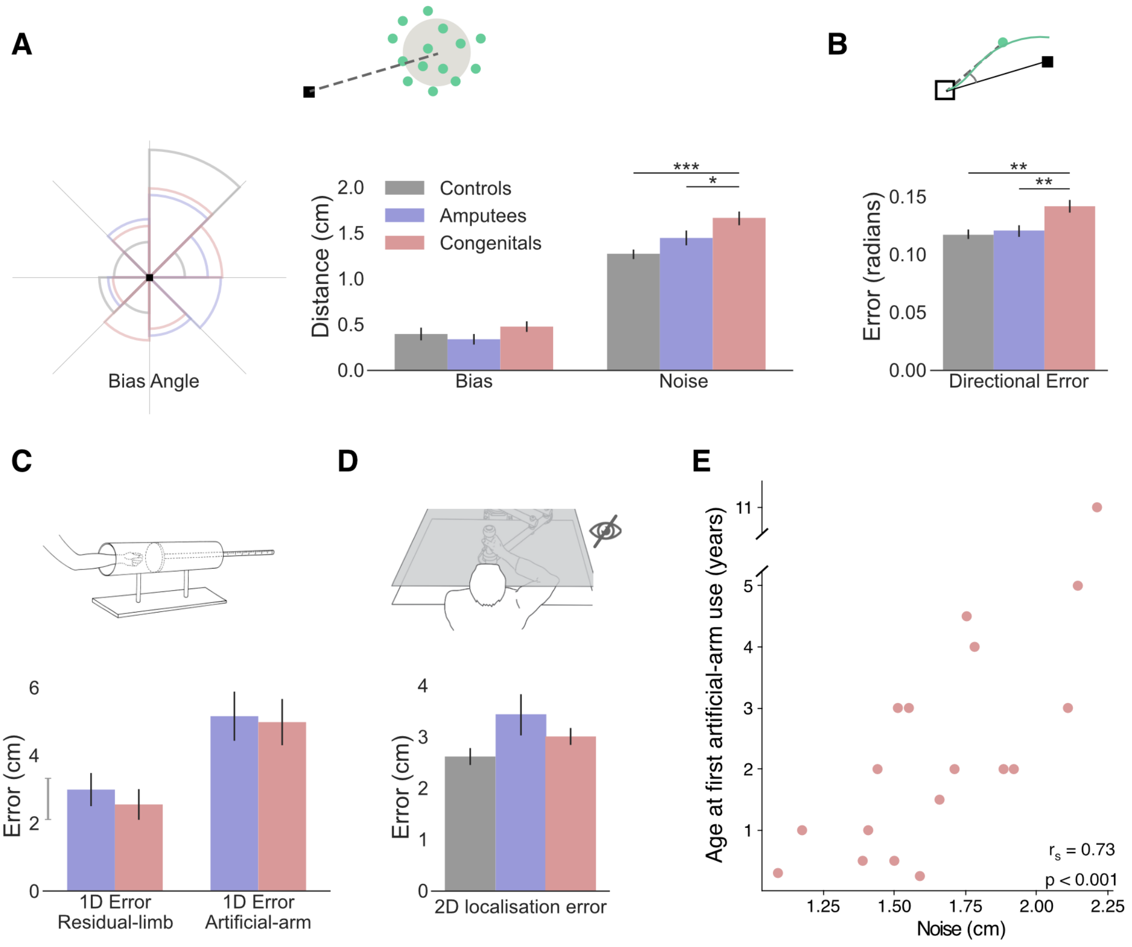


Figure 3.2. *Exploring the source of increased reaching errors using additional analyses and tasks.* In all plots, grey, blue and red represent controls, amputees and congenitals (respectively). (**A**) Left: rose plot density histogram of the distribution of bias angles across the groups, the larger the arc the more individuals from that groups had a bias within the arcs angle range. We found no significant differences in bias angle between the groups (Watson-Williams circular test: $F_{(2,48)}$=1.95, p=0.15). Right: Error bias and noise results. No significant group differences were found for bias ($F_{(2,47)}$=2.40, p=0.1, BF_{Incl}=0.72). Congenital one-handers show significantly more motor noise than amputees and controls ($F_{(2,47)}$=14.15, p<0.001, η_p^2=0.38; post-hoc significance levels are plotted). (**B**) Initial directional error results. Congenital one-handers have larger directional error in the initial phase of reaching ($F_{(2,47)}$=8.01, p<0.001, η_p^2=0.26; post-hoc significance levels are plotted). (**C**) 1D localisation task results. Participants placed their residual-limb or prosthetic arm inside an opaque tube and were asked to assess the location of the limb using their intact arm. We found no localisation differences between amputees and congenital one-handers in either condition (BF_{10}<0.33 for both). The grey line next to the y-axis shows the mean ± s.e.m of controls non-dominant hand localisation errors. (**D**) 2D localisation task results. Using the same apparatus, participants performed reaches to visual targets without receiving visual feedback during the reach. We found no group differences in absolute error ($F_{(2,44)}$=0.71, p=0.5,

BF_{Incl}=0.33). (**E**) Relationship between prosthetic arm motor noise and age at first prosthetic arm use prosthetic arm in congenital one-handers. Illustration in Figure 3.2D was reproduced from Figure 1A*,* Wilson, Wong, & Gribble 2010*,* PLoS ONE*,* published under the Creative Commons Attribution 4.0 International Public License (CC BY 4.0; https://creativecommons.org/licenses/by/4.0/). * $p < .05$, ** $p < .01$, *** $p < .001$

3.2.4 Congenital one-handers and amputees are equally accurate at localising their prosthetic arm without visual feedback

Commercially available prosthetic arms, as the ones used by our participants, currently lack direct sensory feedback, and of most relevance to reaching, proprioceptive feedback. Proprioception, the sense of position and movement of our body, provides an essential input to the sensorimotor system (Sarlegna & Sainburg, 2009; Wolpert et al., 1995). Together with vision it is used to accurately localise the current position of the arm and guides corrective movement during the execution of reaching movements. The lack of proprioception is therefore a reasonable candidate for explaining the inferior control of the prosthetic arm. As a proxy measure for proprioception, we assessed prosthetic arm localisation abilities. First, to assess prosthetic arm localisation, at its most basic and simple form, we tested prosthetic arm localisation along a single axis. In a separate task, participants were asked to place their prosthetic arm in an opaque tube and use their intact arm to point to the end-point of the prosthetic arm (McDonnell et al., 1989); see 3.4 Methods). Since the prosthetic arm is sensed and localised via the residual-limb, we also assessed the proprioception of the residual-limb. Interestingly, we found no localisation differences between amputees and congenital one-handers in either condition (Residual-limb: *Mann-Whitney* W=112.5, p=0.46, BF_{10}=0.26; Prosthetic arm: *Mann-Whitney* W=104.5, p=0.7, BF_{10}=0.24; See Figure 3.2C), suggesting that congenital one-handers are equally able as amputees at localising their prosthetic arm.

While prosthetic arm localisation does not seem to differ between our two limbless groups, it is still possible that the online integration of localisation input, rather than the input itself, is suboptimal in congenital one-handers. To test this, we asked participants to perform a task very similar to our main reaching task, with the exception that participants reached to visual targets without receiving continuous visual feedback of their limb position (see 3.4 Methods). Here, participants were instructed to prioritise accuracy in their performance. Using the same ANCOVA approach described above, we compared prosthetic arm (and non-dominant arm) errors of the three groups, while controlling for intact-hand performance as a covariate. We found no group differences in prosthetic arm errors ($F_{(2,44)}=0.71$, $p=0.5$, $BF_{Incl}=0.33$; See Figure 3.2D). We further performed a planned pairwise comparison between prosthetic arm performance of congenital one-handers and amputees and found no significant difference ($t=0.71$, $p_{unc}=0.48$, $BF_{10}=0.25$). Together, these results suggest that congenital one-handers' prosthetic arm localisation is not substantially different than that of amputees.

3.2.5 Congenital one-handers show larger prosthetic arm initial directional errors

Fast reaching movements, such as the ones performed in our main task, can be roughly divided into two phases: an *initial impulse phase* that involves the execution of a motor plan constructed prior to movement initiation and an *error correction phase* where sensory information is used to correct errors during execution (Elliott et al., 2001). The timing of peak velocity in such a movement is often used as a time-point that mostly reflects the first phase, i.e. the trajectory up to this point is mostly governed by feedforward mechanisms (Krakauer et al., 1999; Patterson et al., 2017; Sainburg et al., 2003). As the error at the end of the reach can originate from both feedforward processes and sensory integration processes, comparing the errors at the initial phase allows us to disentangle feedforward from feedback mechanisms. Specifically, the directional error at this stage provides a measure of how far away the movement is from the target's direction. To measure the initial directional error for each trial we took the direction vector (the line connecting the home position and the arm's location at peak velocity; see Figure 3.2B) and calculated the absolute angle between that direction vector and the target direction vector (the line connecting the target and the home position). While reaching paths are known to diverge from the straight line differently depending on the reach direction (Van Beers et al., 1999, 2004), because we compare directional errors across groups, this measure is suitable for our present purposes. For this reason, we also do not assume the 'optimal' directional error would be zero. We use the initial directional error to characterise the early part of the arm trajectory as an indicator of the accuracy of the motor plan. As with previous measures, initial directional errors were analysed using an ANCOVA comparing directional errors of the prosthetic arm (and non-dominant arm) of the three groups, while controlling for intact-hand directional errors as a covariate. We found significant group differences in prosthetic arm errors ($F_{(2,47)}=8.01$, $p<0.001$, $\eta_p^2=0.26$). Congenital one-handers exhibited larger directional errors with their prosthetic arm compared to amputees ($t=-3.515$, $p=0.003$, Cohen's-$d=-1.10$), and controls ($t=-3.31$, $p=0.005$, Cohen's-$d=-0.98$). Amputees' prosthetic arm directional errors did not differ from those of the nondominant arm of controls ($t=.16$, $p=0.9$, $BF_{10}=0.21$). This result suggests that congenital one-handers' initial motor plan differs from that of amputees and controls. However, based on this measure alone, we are unable to distinguish between errors resulting from the motor plan itself or with noise resulting from its execution.

3.2.6 Early-life but not present experience with prosthetic arms affects current motor control in congenital one-handers

We tested the hypothesis that present prosthetic arm usage will have a significant relationship on users' prosthetic arm motor control. First, we confirmed that although congenital one-handers have accumulated on average ~29 more years of (intermittent) prosthetic arm experience compared to amputees ($t_{(30)}=-7.86$, $p<0.001$), there are no differences in prosthetic arm daily usage between the two prosthetic arm users' groups, as assessed using questionnaires (acquired amputees vs congenital one-handers; $t_{(30)}$=-0.25, p=0.81, BF_{10}=0.35). Contrary to our hypothesis we found no such relationship between prosthetic arm reaching errors and a daily-life prosthetic arm usage score, encompassing both daily wear-time and functionality of use ($r_{(30)}$=-0.05, p=0.78, BF_{10}=0.23). We did, however, find a relationship between daily-life prosthetic arm usage and intact-hand reaching errors across amputees and congenital one-handers ($r_{(39)}$=-0.41, p=0.008; see Supplementary Figure S1). Smaller intact-hand errors (higher accuracy) were associated with higher prosthetic arm use scores (more versatile and frequent use). While being cautious not to infer causality from a correlation, we believe this result uncovers a relationship between an individual's general motor control (as measured by their intact arm) and their ability to use a prosthetic arm. This result further highlights the need to control for individual differences in intact-hand motor control when studying prosthetic arms.

While we found that prosthetic arm present-day use does not predict its motor control (i.e., absolute error in reaching), we wanted to next test whether the user's early-life experience does. Quantifying something as complex as prosthetic arm past use is a difficult feat. Here, we focused on the age at which congenital one-handers were first fitted with a prosthetic arm (range: 2 months – 11 years). Interestingly, we found a significant positive correlation between age at first prosthetic arm use and prosthetic arm reaching errors ($r_{s(16)}$=0.57, p=0.01; see Figure 3.1D). Congenital one-handers who started using a prosthetic arm at an earlier age produced smaller errors with their current prosthetic arm as adults. This result suggests that our ability to adjust our motor representation might not be as flexible as we thought and might be constrained by early life experience. Finally, we did not find a significant relationship between past (age at first prosthetic arm use) and present (daily-life use score) prosthetic arm experience

($r_{s(16)}$=-0.03, p=0.91), or between prosthetic arm reaching errors and elapsed time since first prosthetic arm use ($r_{(16)}$=0.01, p=0.96, BF_{10}=0.29).

3.2.7 Congenital one-handers age at first experience with a prosthetic arm correlates with motor noise

Next, we wanted to test which of the aforementioned measures, each representing a different aspect of motor control, best correlates with age at first prosthetic arm use. Discovering which of these measures are influenced by age at first use can give us an insight into which age-constrained motor control process might be involved in learning to control a prosthetic-limb. Motor noise and initial directional error, being the two measures that produced a significant group effect, are of special interest, but for the sake of completeness we have tested the potential impact of all six measures. We found that only motor noise significantly correlated with age at first prosthetic arm use ($r_{s(16)}$=0.73, p_{bonf}=0.003 [corrected for 6 comparisons]; see Figure 3.2E). That is, individuals who started using a prosthetic arm earlier in life also showed less end-point motor noise in the reaching task. While we did find group differences in initial directional errors (as reported in Results section 3.2.5), it did not significantly correlate with age at first prosthetic arm use ($r_{s(16)}$=0.38, p_{bonf}=0.74). From these results, we infer that early-life experience relates to a suboptimal ability to reduce the system’s inherent noise, and that this is possibly not related to the noise generated by the execution of the motor plan. Therefore, improved motor control, due to early life experience, might relate to suboptimal integration of visual and sensory information within the sensorimotor system.

3.2.8 Amputees' prosthetic arm control might also be constrained by a time-sensitive process following amputation

Finally, we wanted to explore whether amputees also show a parallel phenomenon of an effect of early-life experience of prosthetic arm use on current motor control. From the relationship observed in congenital one-handers, we can draw two predictions with regards to amputees: first, that the age at which you started using a prosthetic arm (even in adulthood) would potentially have an effect on reaching accuracy. So, the younger you were when you learned to use a prosthetic arm the better. However, we found no such correlation between prosthetic arm errors in amputees and age at first prosthetic arm use ($r_{s(12)}$=-0.23, p=0.43).

An alternative parallel to the age at first prosthetic arm use in amputees is the amount of time an individual has spent being limbless before starting to use a prosthetic arm. So, the longer one waits after amputation to start using a prosthetic arm, the bigger their reaching errors would be. Here, we find a significant positive correlation between prosthetic arm absolute errors and years of limbless experience ($r_{s(12)}$=0.71, p=0.005). The sooner an amputee was fitted with a prosthetic arm after amputation, the smaller errors they made with their current prosthetic arm years later. Similarly to congenital one-handers, this relationship appears to be driven by motor noise and not by bias. Motor noise was significantly correlated with years of limbless experience ($r_{s(12)}$=0.85, p_{bonf}=0.03), while bias did not ($r_{s(12)}$=0.32, p_{bonf}=1; comparing between correlations: Z=2.9, p=0.003). This suggests that the link between age of first use and errors in congenital one-handers may not be limited to a developmental period, but to an individual's first experiences as a limbless individual. Alternatively, this finding points towards a possible plasticity window in the time after amputation, where early exposure to a prosthetic arm results in higher levels of control. Although the type of plasticity bottlenecks in each group might be different, it appears that the amount of time an individual spends using their residual limb before starting to use a prosthetic arm has a long-lasting effect, in terms of motor noise, on their ability to control a prosthetic arm.

3.3 Discussion

While infants' reaches are surprisingly functional (Babinsky et al., 2012; von Hofsten, 1980), they take a considerable amount of time to be fine-tuned. There are multiple, non-linear (Olivier et al., 2007) developmental processes occurring until at least the age of ~12 years (Schneiberg et al., 2002; Simon-Martinez et al., 2018; Sveistrup et al., 2008). In this context, it may not be surprising that we found congenital one-handers, who started using a prosthetic arm in early childhood, to perform differently in a visuomotor precision reaching task, relative to acquired amputees, who only began to use a prosthetic arm in adulthood (age *range*=19-56, *mean*=32). Yet, contrary to our expectation, congenital one-handers performed worse than amputees, who in turn did not show any deficits in controlling their prosthetic arm relative to two-handed controls using their nondominant arm. Considering the early prosthetic arm experience of congenital one-handers, and that it coincides with a time in development when the motor system has to constantly adapt as the body (and arms) grow, it is surprising that congenital one-handers under-perform at this straightforward motor task relative to amputees. The observed difference between the two prosthetic arm user's groups, and the fact that increased experience with a prosthetic arm did not lead to better performance, is also in stark contrast with the notion that our internal model flexibly scales with the endpoint of the tool, as we use it (Miller et al., 2018).

What mechanisms might be driving the observed deficits in congenital one-handers? To successfully position the prosthetic arm at the visual target, multiple internal calculations and transformations need to occur, each of which could potentially be impacted by early life experience. First, an internal model of the prosthetic arm needs to be developed or adapted, so as to translate a desired goal into an appropriate motor coordination plan. Our analysis points at potential deficits in this internal model, as congenital one-handers' initial directional error–reflecting the execution of an initial motor plan and thought to precede sensory feedback–is greater than that of amputees. If true, this suggests that congenital one-handers may not be able to refine their model enough to create an accurate template of their prosthetic arm. However, since this deficit was dissociated from our key measure of absolute reaching error, we believe other mechanistic deficits might be at play. With that in mind, a further step for executing a successful reach is being able to integrate concurrent input from the executed plan with online visual feedback of the prosthetic arm, as well as any other relevant somatosensory feedback from the residual arm. We did not find strong evidence that both static or dynamic localisation of prosthetic arm position is impaired in congenital one-handers. As such, by elimination, our evidence suggests that it is the process of integrating visual information that is suboptimal in congenital one-handers. This idea is consistent with previous evidence showing congenital one-handers have impaired processing of visual hand information (See Chapter 1)(Maimon-Mor, Schone, et al., 2020)(Maimon-Mor, Schone, et al., 2020)(Maimon-Mor, Schone, et al., 2020)(Maimon-Mor, Schone, et al., 2020)(Maimon-Mor, Schone, et al., 2020)(Maimon-Mor, Schone, et al., 2020). This interpretation is also compatible with previous studies in individuals experiencing a brief period of postnatal visual deprivation which caused long-lasting (though mild) alterations to visuo-auditory processing (de Heering et al., 2016). While the maturation of the vision system occurs much earlier than that of motor control, the ability to optimally integrate visual information continues to develop way into childhood (Contreras-Vidal, 2006; Contreras-Vidal et al., 2005). Lack of concurrent visual and motor experience during development might therefore cause a deficit in the ability to form the computational substrates and thus to integrate visuomotor information. Indeed, we found that endpoint noise, and not initial directional error, associates with age at first prosthetic arm use. This, too, supports the idea that one's ability to efficiently integrate sensory information with motor control might relate to early life experience with a prosthetic arm.

Perhaps our most intriguing result relates to a relationship between the deficits in motor control (reaching error) and the age in infancy at which congenital one-handers started using a prosthetic arm. Individuals who started using a prosthetic arm for the first time earlier in infancy also showed less motor deficit. The detected relationship between early life development and motor skill in adulthood allows us to address questions about the plasticity of visuomotor control across life. Why would a 4-year-old child have a disadvantage in visuomotor learning relative to a 2-year-old? This could be explained both by how early she picked up prosthetic arm use, or rather, how late she waited before starting to use it. While the two alternatives sound similar, these two complementary explanations can be mechanistically dissociated. The first explanation is that the more experience you have with a prosthetic arm in early childhood, the better you will be at controlling the prosthetic arm as an adult. Based on the well-accepted assumption that the brain is more plastic early in life, this will allow children to acquire the new skill more easily (Knudsen, 2004). Alternatively, templates for motor control of the hand (e.g., driven by genetics) will decay over time if not consolidated by relevant experience-related input (Dempsey-Jones, Wesselink, et al., 2019; Krubitzer & Prescott, 2018). The longer one waits before including the prosthetic arm as part of their motor repertoire, the less she will be able to take advantage of this genetic blueprint, i.e. in terms of brain structure and function (Sur & Rubenstein, 2005). Another, third, explanation relates to the fact that by not wearing a prosthetic arm, congenital one-handers develop alternative strategies to compensate for their missing hand, for example by using their residual-limb. Congenital one-handers are known to be proficient residual-limb users, and our previous research shows that the residual arm benefits from the sensorimotor territory normally devoted to the hand (Hahamy et al., 2017; Makin, Cramer, et al., 2013). We also previously showed that residual-limb use in congenital one-handers impacts larger-scale network organisation in sensorimotor cortex (Hahamy et al., 2015) demonstrating how compensatory strategies can affect neural connectivity and dynamics. In an extreme scenario, using the residual-limb as an effector in early life might anchor it as the reference frame for all upper-limb motor control. We previously found that this has implications on peri-personal space representation in congenital one-handers (Appendix A)(Maimon-Mor et al., 2017)(Maimon-Mor et al., 2017)(Maimon-Mor et al., 2017)(Maimon-Mor et al., 2017). Thus, the later congenital one-handers start wearing their prosthetic arm, the later they start developing an alternative reference frame, that is, learning the computations and transformations required to perform movements with an end effector at the prosthetic arm tip instead of the residual-limb. Another way to think about this competition between alternative strategies is through the prism of 'habits' and the idea that once you have perfected a particular motor solution, it is more difficult to update it to a different strategy. As these multiple mechanisms are not mutually exclusive, it is possible that they all contribute to the observed relationship between age at first prosthetic arm use and reaching errors. Regardless of the specific mechanism, if congenital one-handers sensorimotor processes are optimised for treating the tip of the residual-limb as the end effector, then when wearing a prosthetic arm, they constantly required to transform information from the residual-limb tip to the prosthetic arm tip and vice-versa, for extrapolating where the residual-limb needs to be to get the prosthetic arm tip to a certain target. Similar to skill acquisition of tools, this extra step of transforming information between two spatially removed endpoints may introduce additional noise (integration over space and time).

Amputees, who were born with a complete upper-limb and lost it later in life, did not show similar deficits in prosthetic arm reaching control. Following the rationale outlined above, it stands to reason that having developed an internal model of their arm in childhood, amputees are able to recycle their internal model of their missing arm to accurately control the prosthetic arm. Indeed, there is mounting evidence to suggest that amputees maintain the representation of their missing hand long after amputation (Kikkert et al., 2016; Wesselink et al., 2019). The motor requirements for control over a prosthetic arm are not identical to that of controlling a biological arm, however, from the perspective of the spatial location of the endpoint, the prosthetic arm roughly mimics that of the missing arm. Interestingly, despite not showing a group deficit in control of their prosthetic arm (relative to controls' nondominant arm), we still found that the time they have taken to use the prosthetic arm following their amputation co-varies with prosthetic arm reaching errors. As with the congenital one-handers, this relationship could be explained both by how early one picks up prosthetic arm use, or how late she waits before starting to use it. For example, research in stroke patients suggested that the imbalance triggered by the assault to the brain tissue creates conditions that are favourable for plasticity, and even been referred to as a second sensitive period (Zeiler & Krakauer, 2013). According to this notion, rehabilitation will be most effective within this limited period of plasticity. Similarly, it has been suggested that sensory deprivation can also promote plasticity and learning (Dempsey-Jones, Themistocleous, et al., 2019). Therefore, amputation might cause a cascade that will result in a brief period of increased plasticity that will be more favourable for learning to use a prosthetic arm. Alternatively, we can also consider the competition model described above; if one has already formed a motor strategy (or a habit) for how to perform tasks without the prosthetic arm, this learnt strategy will impact her ability to use the prosthetic arm later on in life. While the reported correlation relies on a smaller sample size and thus should be taken with a little more caution, the fact that overall, amputees do not show systematic deficit relative to controls, indicate that early life experience drives the observed visuomotor deficits in reaching reported here.

To conclude, the fact that congenital one-handers show inferior prosthetic arm performance compared to amputees is surprising considering both the vast capacity for motor learning that humans exhibit and the fact that congenital one-handers have had more experience with a prosthetic arm and from a much younger age. By the process of elimination, we have nominated visuomotor integration to be the most likely cause underlying this motor deficit. However, more work testing this interpretation directly needs to be carried out to consolidate our interpretation. Moreover, we found that early life experience with a prosthetic arm (in the case of congenital one-handers) or early prosthetic arm experience following amputation (in the case of amputees) has a measurable effect on prosthetic arm motor precision in adulthood. In our dataset, early life experience with a prosthetic arm was not a good indicator for successful current prosthetic arm adoption, however our limited sample size and inclusion criteria of only including individuals who currently use a prosthetic arm prevents us for making direct clinical recommendations. The relationship between intact-arm performance and current prosthetic arm use in both congenital one-handers and amputees is also of interest to prosthetic arm rehabilitation and should be taken into account in future studies. In addition, our research provides insight about the neurocognitive bottlenecks that need to be considered when developing future assistive and augmentative technologies.

3.4 Methods

3.4.1 Participants

Forty-four prosthetic arm users were recruited for this study: 21 unilateral acquired amputees (mean age±std = 48.67±12.9, 18 males, 12 with intact right arm), and 23 congenital one-handers (transverse deficiency; age ± std = 46.09±11.22, 11 males, 17 with intact right arm; see Table 1 for full demographic details). Sample size was based on recruitment capacities considering the unique populations we tested. Seven participants were excluded from all analyses: 4 participants with a trans-humeral limb-loss (3 amputees) were not able to perform the tasks with their prosthetic arm. Two participants (1 amputee) had trouble controlling the robotic handle with their prosthetic arm therefore their prosthetic arm reaches data in both tasks has been excluded. Data from all tasks involving the robotic manipulandum of one participant (congenital) was excluded, due to technical issues with the robotic device.

Additionally, twenty age, gender, and handedness matched two-handed controls were recruited for this study (mean age ± std = 42.55 ± 15.5, 11 males, 14 with a dominant right arm). For all analyses, the controls' dominant arm was compared to the intact arm of the prosthetic arm users, and the non-dominant arm was compared to the prosthetic arm. For the sake of brevity, we refer to the dominant arm of controls as the intact-hand and the non-dominant arm as the prosthetic arm.

Participants were recruited to the study between October 2017 and December 2018, based on the guidelines in our ethical approvals (UCL REC: 9937/001; NHS National Research Ethics service: 18/LO/0474), and in accordance with the declaration of Helsinki. The following inclusion criteria were taken into consideration during recruitment: (1) 18 to 70 years old, (2) MRI safe (for the purpose of other tasks conducted in the scanner), (3) no previous history of mental disorders, (4) for congenital one-handers, owned at least one type of prosthesis during recruitment, (5) for acquired amputees, amputation occurred at least 6 months before recruitment. All participants gave full written informed consent for their participation, data storage and dissemination.

3.4.2 Main Task

3.4.2.1 Experimental setup

Participants sat in front of the experimental apparatus on a barber-style chair, with their head leaning against a forehead rest. Participants performed horizontal plane reaches while holding a handle of a robotic manipulandum with either their hand or the prosthetic arm, with the arm strapped to an armrest. A monitor displaying the task was viewed via a mirror, such that participants did not have direct vision of their arm. To further block any vision of the participant's limb a black barber's cape was used to cover their entire upper body, including their elbow and shoulder. Continuous visual feedback of the robotic handle's position (i.e., the intact/prosthetic arm position) was delivered as a 4 *cm* diameter white cursor (representing the handle size) with a 0.3 *cm* diameter circle at the centre. The handle's position was recorded with a sampling frequency of 200 *Hz*.

3.4.2.2 Experimental design

Participants were asked to reach to visual targets while receiving visual feedback of their hand position using each of their arms. To ensure the setup was optimised for prosthetic arm reaches, participants performed the task with their non-dominant/prosthetic arm first. At the beginning of each trial set 6 practice trials (using targets not included in the task target set) were presented to the participant. Practice was repeated until both experimenter and participant were happy that the participant felt comfortable, and the instructions were fully understood.

A trial was initiated once participants placed the cursor within a white square (1.5 *cm* × 1.5 *cm*) indicating the home (start) position (denoted as position [0,0]). Participants were situated so the home position was aligned with their midline. In each trial, participants reached to a visual target (1.5 *cm* × 1.5 *cm* square) presented in one of 60 predefined locations (see Figure 3.1B). At the end of a trial, the target changed colour to blue to indicate the reach has ended and the endpoint position was recorded. To reduce fatigue and experiment duration, participants were then mechanically assisted by the manipulandum moving the handle back to the home position, before the start of the next trial.

To quantify participants' biological and prosthetic arm motor control, participants were asked to perform a single movement to the target and avoid corrective movements. Constant visual feedback of the arm's position was given. To encourage participants to perform fast-reaching movements, a maximum movement time of 1 *sec* per reach was imposed. Movement initiation was defined by arm velocity exceeding 3.5 *cm/s* starting from the time of participants first movement, following the presentation of the target.

3.4.2.3 Data processing and analysis

To identify the end of the first reach in each trial, tangential arm velocities were used to determine movement termination. Velocity data were smoothed using an 8 Hz low-pass Butterworth filter (Przybyla et al., 2013). Movement termination was defined by the first minimum with a velocity smaller than 50% of the peak velocity. We note that very similar results were observed when using the end of the trial (1 *sec* after initiation) as the movement termination time. Individual trials were excluded if they were accidentally initiated, i.e., if movement terminated close to the home position – closer than 2 *cm* or with a y-value (depth) smaller than 1 *cm*; or if the participants did not finish their reach at the end of the allocated time (1 *sec*) – i.e., trials where movement >10 *cm/s* was recorded at the end of the trial. An average of 1.1 and 1.4 trials per participant were excluded for the intact and prosthetic arm respectively, with a range of 0-7. There were no group differences in the number of excluded trials. Prosthetic arm reach data from one amputee and one one-hander were excluded, due to technical issues with the device.

Absolute Euclidean error from the target was used as the main measure (See Figure 3.1A&C). Motor noise (variability) and bias were calculated for each participant, for each arm, by aggregating across all targets. Error vectors of each trial (the line connecting the target with the end-point location) were overlaid as if they were made to a single target (See Figure 3.2A). Bias was defined as the distance from the centre of the overlaid endpoints (calculated as the mean x and mean y of the relative error vectors) to the target. Noise was defined as the spatial standard deviation (SD) of endpoints relative to the same centre of overlaid endpoints. Initial directional error was defined for each trial as the absolute angle between the direction vector–

the line connecting the home position and the arm’s location at peak velocity (see Figure 3.2B); and the direction vector–the line connecting the target and the home position. The arm’s location at peak velocity was used as a proxy for a time-point that mostly reflects the motor planning phase, i.e., feedforward mechanisms, before sensory information is used to correct for errors during execution.

3.4.3 Additional Tasks

3.4.3.1 1D arm localisation

To assess residual-limb and prosthetic arm sense of limb-position, we used a task similar to that described in (McDonnell et al., 1989). Participants were asked to place their residual-limb or prosthetic arm in an opaque tube (see Figure 3.2C). In each trial, an adjustable contact plate was placed at a different position within the tube. Participants were asked to move their arm into the tube until it made contact with the plate. They were then instructed to use their intact arm to mark the estimated location of their tested arm on a paper strip placed on the side of the tube. At the end of the trial, participants were asked to remove their arm from the tube before the start of the next trial. A barber’s cape was used to cover the upper body and arms. For each condition (residual/prosthetic arm), pseudo-randomised 8 distances were used; these were calculated as a percentage of participant’s maximum reach distance (25%-75%). The mean absolute distance between the participant’s estimate and true position was used as a measure of 1D localisation abilities. Two amputees and two congenitals did not take part in this task as it was introduced later in the data collection process.

3.4.3.2 2D arm localisation (reaching without visual feedback)

The 2D arm localisation task was almost identical to our main task, with the exception that participants reached to visual targets without receiving continuous visual feedback of their limb position and were allowed to perform corrective movements. To prevent a perceptive drift from the lack of visual information of limb position, visual feedback of the arm's position was given at the end of the trial when returning to the start position. The cursor only reappeared when the arm was less than 3 *cm* away from the start position. At the beginning of the trial, the cursor disappeared upon movement initiation. Movement termination and the recording of the arm's final position occurred when velocity was less than 3.5 *cm/s* for more than 1 *sec*. Due to the noisier nature of these reaches, each of the 60 targets used in the main task was repeated twice (i.e., a total of 120 trials for each arm).

Absolute Euclidean error from the target was used as the main measure. Individual trials were excluded if they were accidentally initiated (see main task data analysis protocol); or if the trial was suspected as invalid, i.e., movement time was longer than 10 secs or error was larger than 20 cm. An average of 1.35 and 1.5 trials per participant were excluded for the intact and prosthetic arm respectively, with a range of 0-13. There were no group differences in the number of excluded trials. Two participants only produced partial data, missing prosthetic arm reaches of 1 congenital one-hander and dominant arm reaches of 1 control.

3.4.4 Prosthetic arm usage assessment

Participants completed a questionnaire to assess various aspects of their current and past prosthetic arm use. Frequency and functionality of prosthetic arm use were combined to create an overall prosthetic arm usage score (as previously used in (Maimon-Mor, Obasi, et al., 2020a; Maimon-Mor & Makin, 2020; van den Heiligenberg et al., 2017; Van Den Heiligenberg et al., 2018). To determine frequency of use, participants were asked to indicate the typical number of hours per day, and days per week, they use their prosthetic arm. These were then used to determine the typical number of hours per week that the prosthetic arm was worn. To determine functionality of prosthetic arm use, participants were asked to complete the prosthetic arm activity log (Prosthesis Activity Log - PAL) , a modified version of the Motor Activity Log (MAL) questionnaire, which is commonly used to assess arm functionality in those with upper-limb impairments (Uswatte et al., 2006). The PAL consists of a list of 27 daily activities (see https://osf.io/jfme8/); participants rated how often they incorporate their prosthetic arm to complete each activity on a scale of "never" (0 points), "sometimes" (1 point) or "very often" (2 points). The PAL score is then calculated as the sum of all points divided by the maximum possible score, generating a value between 0 (no functionality) and 1 (maximum functionality). Prosthetic arm scores were calculated for the most used prosthetic arm, wear time and PAL were standardised using a Z-transform and summed to create a prosthetic arm usage score that reflects frequency of use and incorporation of the prosthetic arm in activities of daily living. These measures have been previously shown to have good reliability using a test-retest assessment (Maimon-Mor, Obasi, et al., 2020a).

Congenital one-handers were asked to report the age at which they first used a prosthetic arm. Two participants (AC16, AC17) were assigned a value of one year after responding: "months old" and "less than a year" respectively. Acquired amputees were asked to report the time after amputation in which they were fitted with their first prosthetic arm. Two participants (AA13, AA19) were assigned a value of one year after responding: "same year, few months after amputation" and "A few months after amputation" respectively.

3.4.5 Statistical analyses

Statistical analyses were carried out using JASP (Jasp Team, 2020) An analysis of covariance (ANCOVA) was used to test group differences for all measures in which we had recorded performance of both arms (i.e., all measures but 1D localisation). The prosthetic arm performance was the dependent variable, intact-hand performance was defined as a covariate and group (controls, amputees, and congenitals) as a between-subject variable. Post-hoc group tests were corrected for multiple comparisons (Tukey correction). Absolute error measures were logarithmically transformed and then averaged in order to correct for the skewed error distribution and satisfy the conditions for parametric statistical testing. Outliers were defined as 1.5 times the IQR (interquartile ranges) below the first quartile or above the third quartile of the transformed error. Following this outlier criteria, in the main task, 2 participants (1 amputee, 1 congenital one-hander) were excluded due to their high prosthetic arm errors. For the 2D localisation task, 3 participants (2 amputees, 1 control) were excluded due to their high intact-arm errors. In parametric analyses (ANCOVA, ANOVA, Pearson correlations), where the frequentist approach yielded a non-significant p-value, a parallel Bayesian approach was used and Bayes Factors (*BF*) were reported (Morey & Rouder, 2015; Rouder et al., 2009, 2012, 2016). A $BF<0.33$ is interpreted as support for the null-hypothesis, $BF > 3$ is interpreted as support for the alternative hypothesis (Dienes, 2014). In Bayesian ANOVAs and ANCOVA's the inclusion Bayes Factor of an effect (BF_{Incl}) is reported, reflecting that the data is X (*BF*) times more likely under the models that include the effect than under the models without this predictor. When using a Bayesian t-test, a Cauchy prior width of 1.39 was used, this was based on the effect size of the main task, when comparing prosthetic arm reaches of amputees and congenital one-handers. Therefore, the null hypothesis in these cases would be there is no effect as large as the effect observed in the main task. Parametric analyses were used if assumptions (e.g., for normality) were met, otherwise a Spearman correlation/Mann-Whitney were used. Since the Spearman correlation has, to our knowledge, no current Bayesian implementation no BF values are reported for these tests. The Parametric Watson-Williams multi-sample test for equal means was used as a one-way ANOVA test for bias angular data.

Participant	Age	Y Since Amp	Gender	Amp Side	Amp level	Amp cause	Prosthetic arm Type	Prosthetic arm wear time	PAL	Usage Score	Age at first prosthetic arm use	Years of limbless experience	Residual-limb length
AA01	58	14	M	L	TR	Trauma	Myo	119	0.5	1.87		0.5	15
AA02	46	16	F	L	TR	Trauma	Myo	56	0.59	0.49		0.5	14
AA03*	50	3	F	L	TR	Trauma	Mech	77	0.44	0.44			18
AA04*	53	34	M	L	TH	Trauma	Mech	48	0.2	-1.4		0.33	
AA05	21	1	M	R	TR	Trauma	None	0	0.04	-3.44		0.083	34
AA06*	42	18	M	R	TR	Trauma	Cosm	35	0.07	-2.33			16
AA07	61	21	M	L	TR	Trauma	Cosm	105	0.67	2.21		0.125	29.5
AA08	60	42	M	R	TR	Trauma	Mech	87.5	0.28	0.05		3.5	9
AA09*	65	37	M	R	TH	Trauma	Mech	98	0.46	1.11		0.25	
AA10*	47	21	M	R	TH	Trauma	Cosm	84	0.3	0.03		1	
AA11	68	12	M	L	TR	Trauma	Mech	35	0.54	-0.31		0.33	21.5
AA12	49	5	M	R	TR	Vascular disease	Cosm	42	0.59	0.1		0.5	20
AA13	57	29	M	L	TR	Trauma	Mech	65	0.11	-1.31		1	18
AA14	53	33	M	L	TR	Trauma	Myo	98	0.43	0.98		0.67	12
AA15*	28	10	F	R	TR	Trauma	Mech	2	0	-3.55		5	7.5
AA16	29	11	M	L	TR	Trauma	None	0	0	-3.61		2	28.5
AA17	43	20	M	R	TR	Trauma	Myo	98	0.61	1.75		0.083	8
AA18	55	12	M	L	TR	Trauma	Myo	98	0.65	1.92		0.5	33
AA19	61	17	M	L	TR	Trauma	Mech	91	0.74	2.11		1	18
AA21	30	3	M	L	TR	Trauma	Myo	49	0.59	0.29		0.54	20.5
AC01	51		F	L	TR	Congenital	Cosm	7	0.26	-2.3	0.5		10
AC02	47		M	L	TR	Congenital	Mech	84	0.7	1.75	1		13
AC03	45		F	L	TR	Congenital	Myo	63	0.46	0.13	4.5		8
AC04*	26		M	L	TR	Congenital	Mech	6	0.13	-2.88	0.25		15
AC05*	55		F	L	TR	Congenital	Cosm	112	0.3	0.82	0.25		6

AC06	63	M	L	TR	Congenital	Cosm	87.5	0.35	0.35	2	10
AC07	35	M	L	TR	Congenital	Cosm	56	0.28	-0.84	3	11
AC09	49	M	L	TR	Congenital	Myo	91	0.57	1.39	2	21
AC10	42	M	L	TR	Congenital	Cosm	56	0.54	0.28	2	10.5
AC11	66	F	R	TR	Congenital	Cosm	42	0.35	-0.93	5	9
AC12	56	F	R	TR	Congenital	Cosm	98	0.43	0.98	3	11.5
AC13*	53	M	L	TH	Congenital	Mech	63	0.33	-0.43	2	
AC14	42	M	L	TR	Congenital	Mech	2	0.09	-3.17	4	12
AC15	55	F	L	TR	Congenital	Myo	105	0.65	2.12	3	11.5
AC17	29	M	L	TR	Congenital	Myo	70	0.46	0.33	1	12
AC18	53	F	L	TR	Congenital	Cosm	48	0.65	0.52	1.5	7
AC20	52	F	R	TR	Congenital	Myo	32.5	0.26	-1.58	0.3	11.5
AC21	32	F	R	TR	Congenital	Myo	40	0.41	-0.73	0.5	9
AC22	57	M	R	TR	Congenital	Mech	126	0.69	2.88	2	15.5
AC23	47	F	L	TR	Congenital	Myo	84	0.89	2.56	11	8.5
AC25	41	M	L	TR	Congenital	Myo	112	0.85	3.17	0.25	8
CO01	28	F	L								
CO03	40	F	L								
CO04	59	M	L								
CO05	27	F	R								
CO06	61	F	L								
CO07	35	M	L								
CO08	34	F	L								
CO09	24	M	L								
CO10*	70	M	L								
CO11	24	M	L								
CO12	18	F	L								

CO13	67	M	L
CO14	50	M	R
CO15	51	F	L
CO16	36	F	L
CO17	41	M	R
CO18	33	M	R
CO19	45	M	R
CO20	54	M	R
CO21	53	M	L

Table 3.1. Demographic details of all participants. Participant: AA = acquired amputee, AC = congenital one-hander, CO = two-handed control; participants marked with an asterisk have valid data only for their intact-hand and were therefore excluded from most analyses. Y since amp = years since amputation. Gender: M = male, F = female. Amp Side = side of limb loss or non-dominant side: L = left, R = right. Amp level = level of limb loss: TR = trans-radial, TH = trans-humeral. Prosthetic arm type = preferred type of prosthetic arm: Cos = cosmetic, Mech = mechanical, Myo = myo-electric. Prosthetic arm wear time = typical number of hours prosthetic arm worn per week. PAL = functional ability with a prosthetic arm as determined by PAL questionnaire (0 = minimum function, 1 = maximum function). Usage Score = Prosthetic arm usage score combining wear time and PAL. Age at first prosthetic arm use = Age at which congenital one-handers were first introduced to a prosthetic arm. Years of limbless experience = Time after amputation at which amputees were first introduced to a prosthetic arm. Residual-limb length = measured in cm.

Discussion

4.1 Thesis overview

This thesis comprises of a set of experiments designed to provide a better understanding of the neural and cognitive resources used to support upper-limb prosthesis use. As prosthetic limbs are designed and used as body part substitutions, technological embodiment was a useful framework to guide this examination. I employed a variety of tasks and measurement tools to provide different levels of explanations to the question: can one-handed individuals harness hand-related resources to support their prosthetic-limb?

In Chapter 1 I show that congenital one-handers differ from amputees in how they process visual hand information. I argue that this disparity most likely arises from differences in motor hand resources and in the ability to simulate hand postures. Having atypical available motor hand resources might therefore lead congenital one-handers to differ from amputees in prosthetic-limb use. In Chapter 2 I show that visual prosthesis representation in the extra-striate body area of both congenitals and amputees changes with increasing levels of prosthesis use. Challenging the naïve notion of *neural embodiment*, prosthesis representation did not become more similar to hand representation but instead a new neural category of prosthetic devices was formed. In Chapter 3 I show that certain aspects of sensorimotor upper-limb behaviour depend on early life experience with either an artificial (prosthesis) or a biological arm. In other words, prosthetic limbs are possibly controlled in a similar way to biological limbs (*cognitive embodiment*), however the ability to produce this “embodied” behaviour as an adult depends on one’s childhood experience.

Before concluding and discussing the broader implications of my findings, I will briefly summarise the additional published work appended to this thesis. This work provides further context to the crucial multidisciplinary approach I have taken in detangling the complex phenomenon of prosthetic-limb use and in mapping how hand-related processes are affected by hand-absence.

4.1.1 Appendix A overview – Peripersonal hand representation

Object manipulation requires continuous visuo-motor transformations between the absolute location of an object in space and its relative location to our hand. Therefore, successful limb use depends on spatial representation of objects surrounding the hand in action-space coordinates. The study presented in Appendix A examines the effect of hand-absence on visuospatial representation and more specifically, the representation of peri-(missing)-hand space in amputees and congenital one-handers. Using fMRI, I show that objects presented near the handless (residual) arm of congenital one-handers engages known peri-hand network brain areas, whereas amputees' handless arm did not significantly engage these areas. One possible interpretation of these results is that the plasticity of these visuospatial processes is limited; since congenital one-handers were born without a hand it is possible that this representation has developed to represent objects in relation to their residual arm (i.e., the reference point of this representation is the end of the residual arm). The peri-hand representation in amputees, however, developed to represent objects relative to their hand. Following amputation, to maintain the same functionality the reference point of this representation needs to shift from the spatial location of the missing hand to the residual arm. The lack of significant activations in amputees might therefore be due to the limited ability of this representation to adapt to the residual arm being the new reference point for action. As discussed in Chapter 3, this has implications on prosthetic-limb use as well, as the point of reference needs to regularly shift between the prosthesis tip and the residual arm when the prosthesis is worn or taken off.

4.1.2 Appendix B overview – Neural embodiment in expert tool users

In Chapter 2, I show that expertise with prostheses pushes their neural representation in the occipitotemporal cortex to be dissociated from both hands and tools. However, following this study one outstanding question remains: is this observed representational shift specific to prosthesis users or is it a more general phenomenon that can be observed in any type of tool use? The study presented in Appendix B was designed in response to this question. In this study, we recruited a group of expert tool users (London litter pickers) as well as novice tool users. Interestingly, expert tool users showed a similar representational shift to the one observed in prosthesis users. In experts compared to novices, the litter-picker tool becomes more dissimilar to hands, suggesting that extensive tool use (with either a prosthesis or a litter-picker) leads to an increased neural differentiation between visual representations of hands and tools.

4.1.3 Appendix C overview – Communicate prosthesis gestures

Hand movements can generally be categorised into two distinct types: actions – meant to manipulate our environment and achieve certain goals, and gestures – meant to communicate ideas and accompany speech. Previous studies assessing prostheses as hand substitutes have focused primarily on prosthesis dexterity in actions (e.g., grasping and manipulating objects), neglecting the hands' key role in communication. In the study in Appendix C, I propose that communicative gestures can be used as an implicit measure of *embodiment*. I show that prosthesis gesture behaviour relates to both its daily functional use and *phenomenological embodiment*.

4.2 General discussion

The scope of the studies described above goes beyond the initial clinical motivation of understanding the neural and cognitive aspects of prosthesis use to promote prosthesis adoption. The experimental results and theoretical frameworks presented can inform basic neuroscience and deepen our knowledge of the principles underlying the plasticity of body representation. Moreover, with the increasing popularity of wearable technology, similar approaches and measures to the ones used here can be adapted to study other devices, and conclusions can be generalised beyond prosthetic-limbs. In what follows I will discuss the relevance of my work to these three perspectives: (1) Clinical, (2) Brain plasticity, and (3) Wearable technology.

4.2.1 Clinical perspective

To date, prosthetic limb fitting is the primary approach to helping individuals regain some of the functionality lost due to hand-absence. While the reasons underlying low prosthesis usage remain unknown (Biddiss & Chau, 2007a; Østlie et al., 2012), substantial efforts are being concentrated on creating sophisticated prostheses (Petrini et al., 2019; Rekant et al., 2020; Resnik et al., 2014), ignoring the fact that the root cause of the problem might lay outside technological development. Although the studies presented in this thesis were not designed to directly inform clinical practice, their results can offer insight that might be useful in developing future clinical approaches. The following, therefore, are merely suggestions for future research directions that might ultimately translate to changes in clinical practice.

Results presented in Chapter 3 point toward two possible limiting factors for prosthesis adoption: fitting time and individual differences in motor abilities. Fitting time relates to the age at which an individual was first fitted with a prosthesis in congenitals, and the time from amputation to prosthesis fitting in amputees. Validating previous questionnaire observations (Biddiss & Chau, 2008), early fitting time in both congenital one-handers and amputees led to more accurate control of the prosthesis, either due to habit or to neural plasticity mechanisms. Based on these findings, one recommendation could be to prioritise early fitting over the introduction of a complex prosthesis to minimise prosthesis abandonment, and to transition to more complex devices over time. Reassuringly, across all studies presented here, the type of device used did not seem to have an effect on control, representation or functional use of the prosthesis. This is encouraging from a clinical perspective as access to motorised prostheses is often limited, especially in rural or underdeveloped areas.

Unlike fitting time, individual differences in motor and cognitive abilities are more commonly overlooked in the study of prosthetic limbs. In empirical research it is known that given the exact same task, individuals will vary greatly in their speed, initial performance and learning rates (Kanai & Rees, 2011; Stark-Inbar et al., 2017). The idea that an individual's predispositions would affect their probability of becoming a successful prosthesis user is not a new one (Biddiss & Chau, 2007a). However, previous research has mostly been limited to demographic, social and physical factors. In Chapter 3 I show that intact hand performance significantly relates both to prosthetic arm performance and to daily prosthesis use. Future studies should therefore make greater efforts to measure individuals' abilities independent of prosthesis use and identify key aspects that might limit prosthesis adoption. In the future, the decision of which prosthesis type to fit an individual can be aided by assessments, and prosthesis companies should make an effort to ensure the reliance on these abilities is minimised in the device's design.

4.2.2 Brain plasticity perspective

Brain plasticity is a term used to define the brain's ability to change and adapt throughout one's lifespan. While we are able to learn new skills and form new memories in adulthood, more significant changes such as brain reorganisation (following injury or disease for example) have been shown to be highly restrictive (Haak et al., 2015; Makin & Bensmaia, 2017). Congenital one-handers and amputees provide a useful model in the study of human brain plasticity. As demonstrated in all three chapters, their experiences afford unique opportunities to examine questions relating to sensitive developmental periods, flexibility of body representation, reorganisation following input loss and reorganisation to support new compensatory strategies.

In at least one aspect I found evidence of experience-dependent plasticity. In the visual domain, experience with prostheses resulted in a novel formation of a 'prosthesis' category (Chapter 2). This visual categorical plasticity was observed in both congenital one-handers and amputees, meaning it was affected by current experience and not limited by developmental processes. This work further advances our current understanding of how categorical selectivity emerges in high-level visual cortex (Gomez et al., 2019). These visual areas play an important role in how we make sense of the complex visual world around us and in our ability to cope with the enormous amount of information that falls onto our retina (Kravitz et al., 2013). Therefore, it stands to reason that to be able to adapt to an ever-changing visual world, it is paramount that our representation of that world would change as well. Contrarily, our bodies do not dramatically change through the years, therefore it is perhaps not surprising that sensorimotor brain areas do not show the same level of plasticity as high-level visual cortex (Makin & Bensmaia, 2017; Wesselink et al., 2019). The results presented in Chapter 1 show how bodily visual processes depend on motor resources and thereby how the limited nature of motor plasticity can have implications beyond motor behaviour. In line with previous research, I found further suggestive evidence of the restricted nature of motor plasticity in adulthood (Chapter 3). In my opinion, it is astounding that congenital one-handers' decades of experience using prosthetic devices was still not enough to close the gap and preform simple reaching movements at the same level as their peers (both amputees and controls).

The importance of early life experience demonstrated in Chapter 3 opens the door to several fascinating future research directions. Studying the use of substitution devices in children can be used to answer important questions on the developmental sensitive period for sensorimotor body representation. Examples of such questions are: How does early experience with a substitutive device affect the way it is neurally supported (or embodied)? What conditions need to be met by a substitution device, such as an artificial arm, to be able to support a more "typical" neural development? Are different aspects of the sensorimotor system more sensitive to different features of the device (such as appearance, or control mechanism)? These neuroscientific investigations would not only better our understanding of brain plasticity, body representation and development but could also guide the development and design of future technology.

4.2.3 Wearable technologies perspective

In recent decades technology has become an integral part of almost all everyday activities. A special subset of devices, still not widely used, aim to expand not only our mental capacities (as smartphones do), but our physical ones too. These devices include exoskeletons (Kwak et al., 2015; Soekadar et al., 2016), extra fingers (Kieliba et al., 2020; Wu & Asada, 2015) and limbs (Penaloza & Nishio, 2018), just to name a few. Lessons from prosthetic limbs, as the most widely used wearable motor devices to date, can be used to guide future development and study of wearable devices.

Perhaps the most transferrable aspect of this thesis to the field of wearable technologies is the methodological approach of studying the different levels of embodiment. Measures of *neural* (Chapter 2), *cognitive* (Chapter 3 and Appendix C) and *phenomenological* (Appendix C) embodiment included here can be easily adapted to test other devices, and results presented here can be used as a point of reference.

Results presented here can also guide the design of wearable technology. As mentioned before, the lack of difference between prosthesis types can be interpreted as further evidence against the importance of biomimicry for embodiment. Furthermore, individual differences in abilities as well as individual differences in strategies of device use should be considered in the device's development process. Specifically, when developing intricate control schemes, engineers should bear in mind that not all individuals will be able to learn to use extremely complex systems.

Finally, perhaps the most relevant aspect for crosspollination between the fields in this context, the study of embodiment of prosthetic limbs should be used to assess how important embodiment actually is for wearable technology design and research. This is the topic of the following and final section of this thesis.

4.3 Concluding remarks – is embodiment a useful framework for the study of prosthetic limbs?

In this thesis I attempted to disentangle the obscure concept of prosthesis embodiment. "Does the prosthesis become a body part?" is a philosophically intriguing yet empirically elusive question (Makin et al., 2017, 2020). On the *phenomenological* level, when asked to rate their agreement with a series of embodiment questions such as: "I feel like the prosthesis is a part of my body," prosthesis users only marginally, but significantly, agreed (Appendix C). However, these types of questionnaires are known to be prone to various biases (Lush, 2020; Lush et al., 2020). For example, a prosthesis user might assume the experimenter wants them to say the prosthesis feels like a body part and respond more positively to please them. On the *neural* and *cognitive* levels, beyond the general intuition of resource recycling presented here, there has been no direct evidence that an embodied adoption of a prosthesis would be superior to a non-embodied one. If it is lost functional capabilities we are looking to regain with prostheses, is the focus on embodiment even justified? Should embodiment continue to be the golden standard for wearable technology, or should we simply focus on high functionality? It is often assumed that higher embodiment would result in better use, however that causality has thus far not been directly tested. This distinction, between embodiment and functional utility, exposes one of the biggest problems of relying on technological embodiment as a framework for prosthesis research. While this distinction might seem nuanced, transitioning away from the embodiment framework could create a paradigm shift I believe this field needs. Makin, de Vignemont and Micera (2020) propose dividing the term embodiment into two levels: 'hard embodiment', equivalent to the one described here, in which the objective is for prosthetic limbs to become body parts; and 'soft embodiment', where the objective is to repurpose body related resources to support functions that don't necessarily directly match the biological function of the body. A more radical approach would be to abandon the term 'embodiment' altogether and use other previously established frameworks such as tool use or motor learning.

Nonetheless, there is something about how we feel towards our bodies that is more abstract and goes beyond its usefulness. This emotional attachment is what I believe most people intuitively associate with the term embodiment. To fully understand the significance of this aspect of *phenomenological* embodiment on prosthetics and other wearable technologies, future studies should focus on empirically decoupling functionality from embodiment. One option might be comparing designs that "feel" better even though they are relatively useless, with designs that are very useful but don't generate the same emotional reaction.

References

Adolph, K. E., & Franchak, J. M. (2017). The development of motor behavior. In *Wiley Interdisciplinary Reviews: Cognitive Science* (Vol. 8, Issues 1–2). Wiley-Blackwell. https://doi.org/10.1002/wcs.1430

Aglioti, S. M., Cesari, P., Romani, M., & Urgesi, C. (2008). Action anticipation and motor resonance in elite basketball players. *Nature Neuroscience*, *11*(9), 1109–1116. https://doi.org/10.1038/nn.2182

Amoruso, E., Kromm, M., Spampinato, D., Kop, B., Muret, D., Rothwell, J., Rocchi, L., & Makin, T. R. (2021). Stimulating the deprived motor 'hand' area causes facial muscle responses in one-handers. *Brain Stimulation*, *14*(2), 347–350. https://doi.org/10.1016/j.brs.2021.01.022

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007a). *Non-linear optimisation FMRIB Technial Report TR07JA1.*

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007b). *Non-linear registration aka Spatial normalisation FMRIB Technial Report TR07JA2.*

Antfolk, C., D'Alonzo, M., Rosén, B., Lundborg, G., Sebelius, F., & Cipriani, C. (2013). Sensory feedback in upper limb prosthetics. *Expert Review of Medical Devices*, *10*(1), 45–54. https://doi.org/10.1586/erd.12.68

Archer, D. B., Kang, N., Misra, G., Marble, S., Patten, C., & Coombes, S. A. (2018). Visual feedback alters force control and functional activity in the visuomotor network after stroke. *NeuroImage: Clinical*, *17*, 505–517. https://doi.org/10.1016/j.nicl.2017.11.012

Astafiev, S. V, Stanley, C. M., Shulman, G. L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nature Neuroscience*, *7*(5), 542–548. https://doi.org/10.1038/nn1241

Babinsky, E., Braddick, O., & Atkinson, J. (2012). Infants and adults reaching in the dark. *Experimental Brain Research*, *217*(2), 237–249. https://doi.org/10.1007/s00221-011-2984-5

Beauchamp, M. S., LaConte, S., & Yasar, N. (2009). Distributed representation of single touches in somatosensory and visual cortex. *Human Brain Mapping*, *30*(10), 3163–3171. https://doi.org/10.1002/hbm.20735

Beckerle, P., Kirchner, E. A., Christ, O., Kim, S.-P., Shokur, S., Dumont, A. S., Kõiva, R., Bekrater-Bodmann, R., Dosen, S., Abbink, D. A., Castellini, C., & Lenggenhager, B. (2018). Feel-Good Robotics: Requirements on Touch for Embodiment in Assistive Robotics. *Frontiers in Nerorobotics*, *12*(84), 1–7. https://doi.org/10.3389/fnbot.2018.00084

Bekrater-Bodmann, R. (2020). Perceptual correlates of successful body-prosthesis interaction in lower limb amputees: psychometric characterization and development of the Prosthesis Embodiment Scale. *Scientific Reports*, *10:14203*. https://doi.org/10.31234/osf.io/7wqrc

Belongie, S., Malik, J., & Puzicha, J. (2002). Shape Matching and Object Recognition Using Shape Contexts. *IEEE Transactions on Pattern Analysos and Machine Intelligence*, *24*(24), 509–522. https://doi.org/doi:10.1109/34.993558

Bensmaia, S. J., & Miller, L. E. (2014). Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nature Reviews Neuroscience*, *15*(5), 313–325. https://doi.org/10.1038/nrn3724

Berthier, N. E., & Keen, R. (2006). Development of reaching in infancy. *Experimental Brain*

Research, *169*(4), 507–518. https://doi.org/10.1007/s00221-005-0169-9

Bestmann, S., Oliviero, A., Voss, M., Dechent, P., Lopez-Dolado, E., Driver, J., & Baudewig, J. (2006). Cortical correlates of TMS-induced phantom hand movements revealed with concurrent TMS-fMRI. *Neuropsychologia*, *44*(14), 2959–2971. https://doi.org/10.1016/j.neuropsychologia.2006.06.023

Biddiss, E., & Chau, T. (2007a). The roles of predisposing characteristics, established need, and enabling resources on upper extremity prosthesis use and abandonment. *Disability & Rehabilitation: Assistive Technology*, *2*(2), 71–84. https://doi.org/10.1080/17483100601138959

Biddiss, E., & Chau, T. (2007b). Upper limb prosthesis use and abandonment: A survey of the last 25 years. *Prosthetics and Orthotics International*, *31*(3), 236–257. https://doi.org/10.1080/03093640600994581

Biddiss, E., & Chau, T. T. (2008). Multivariate prediction of upper limb prosthesis acceptance or rejection. *Disability & Rehabilitation: Assistive Technology*, *3*(4), 181–192. https://doi.org/10.1080/17483100701869826

Bilalić, M., Grottenthaler, T., Nägele, T., & Lindig, T. (2016). The Faces in Radiological Images: Fusiform Face Area Supports Radiological Expertise. *Cerebral Cortex*, *26*(3), 1004–1014. https://doi.org/10.1093/cercor/bhu272

Bloomer, C., & Kontson, K. L. (2020). Comparison of DEKA Arm and Body-Powered Upper Limb Prosthesis Joint Kinematics. *Archives of Rehabilitation Research and Clinical Translation*, *2*(3), 100057. https://doi.org/10.1016/j.arrct.2020.100057

Bracci, S., Caramazza, A., & Peelen, M. V. (2015). Representational Similarity of Body Parts in Human Occipitotemporal Cortex. *The Journal of Neuroscience*, *35*(37), 12977–12985. https://doi.org/10.1523/JNEUROSCI.4698-14.2015

Bracci, S., Cavina-Pratesi, C., Ietswaart, M., Caramazza, A., & Peelen, M. V. (2012). Closely overlapping responses to tools and hands in left lateral occipitotemporal cortex. *Journal of Neurophysiology*, *107*(5), 1443–1456. https://doi.org/10.1152/jn.00619.2011

Bracci, S., & Peelen, M. V. (2013). Body and object effectors: The organization of object representations in high-level visual cortex reflects body-object interactions. *Journal of Neuroscience*, *33*(46), 18247–18258. https://doi.org/10.1523/JNEUROSCI.1322-13.2013

Braunlich, K., Liu, Z., & Seger, C. A. (2017). Occipitotemporal Category Representations Are Sensitive to Abstract Category Boundaries Defined by Generalization Demands. *The Journal of Neuroscience*, *37*(32), 7631–7642. https://doi.org/10.1523/JNEUROSCI.3825-16.2017

Braunlich, K., & Love, B. C. (2018). Occipitotemporal representations reflect individual differences in conceptual knowledge. *Journal of Experimental Psychology: General*, *Advance on*. https://doi.org/10.1037/xge0000501

Brozzoli, C., Makin, T. R., Cardinali, L., Holmes, N. P., & Farnè, A. (2011). Peripersonal space: A multisensory interface for body-object interactions. In *The Neural Bases of Multisensory Processes* (pp. 449–465). CRC Press/Taylor & Francis. http://www.ncbi.nlm.nih.gov/pubmed/22593895

Brugger, P. (2012). Phantom limb, phantom body, phantom self: a phenomenology of “body hallucinations". In *Hallucinations* (pp. 203–218). Springer.

Bruno, V., Ronga, I., Fossataro, C., Capozzi, F., & Garbarini, F. (2019). Suppressing movements with phantom limbs and existing limbs evokes comparable electrophysiological inhibitory responses. *Cortex*, *117*, 64–76. https://doi.org/10.1016/j.cortex.2019.02.024

Bruurmijn, M. L. C. M., Pereboom, I. P. L., Vansteensel, M. J., Raemaekers, M. A. H., & Ramsey, N. F. (2017). Preservation of hand movement representation in the sensorimotor areas of amputees. *Brain*, *140*(12), 3166–3178. https://doi.org/10.1093/brain/awx274

Carey, S. L., Lura, D. J., & Highsmith, M. J. (2017). Differences in Myoelectric and Body-Powered Upper-Limb Prostheses. *Journal of Prosthetics and Orthotics*, *29*, P4–P16. https://doi.org/10.1097/jpo.0000000000000159

Chao, L. L., & Martin, A. (2000). Representation of Manipulable Man-Made Objects in the Dorsal Stream. *NeuroImage*, *12*(4), 478–484. https://doi.org/10.1006/nimg.2000.0635

Choi, H. J., Zilles, K., Mohlberg, H., Schleicher, A., Fink, G. R., Armstrong, E., & Amunts, K. (2006). Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. *Journal of Comparative Neurology*, *495*(1), 53–69. https://doi.org/10.1002/cne.20849

Cisek, P. (2007). Cortical mechanisms of action selection: the affordance competition hypothesis. *Phil. Trans. R. Soc.*, *362*, 1585–1599. https://doi.org/10.1098/rstb.2007.2054

Cisek, P., & Kalaska, J. F. (2010). Neural Mechanisms for Interacting with a World Full of Action Choices. *Annual Review of Neuroscience*, *33*(1), 269–298. https://doi.org/10.1146/annurev.neuro.051508.135409

Cisek, P., & Pastor-Bernier, A. (2014). On the challenges and mechanisms of embodied decisions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1655). https://doi.org/10.1098/rstb.2013.0479

Cohen, L. G., Bandinelli, S., Findley, T. W., & Hallett, M. (1991). Motor reorganization after upper limb amputation in man: A study with focal magnetic stimulation. *Brain*, *114*(1), 615–627. https://doi.org/10.1093/brain/114.1.615

Collins, K. L., Guterstam, A., Cronin, J., Olson, J. D., Ehrsson, H. H., & Ojemann, J. G. (2017). Ownership of an artificial limb induced by electrical brain stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(1), 166–171. https://doi.org/10.1073/pnas.1616305114

Conson, M., Mazzarella, E., Frolli, A., Esposito, D., Marino, N., Trojano, L., Massagli, A., Gison, G., Aprea, N., & Grossi, D. (2013). Motor Imagery in Asperger Syndrome: Testing Action Simulation by the Hand Laterality Task. *PLoS ONE*, *8*(7), 1–7. https://doi.org/10.1371/journal.pone.0070734

Conson, M., Pistoia, F., Sarà, M., Grossi, D., & Trojano, L. (2010). Recognition and mental manipulation of body parts dissociate in locked-in syndrome. *Brain and Cognition*, *73*(3), 189–193. https://doi.org/10.1016/j.bandc.2010.05.001

Contreras-Vidal, J. L. (2006). Development of forward models for hand localization and movement control in 6- to 10-year-old children. *Human Movement Science*, *25*(4–5), 634–645. https://doi.org/10.1016/j.humov.2006.07.006

Contreras-Vidal, J. L., Bo, J., Boudreau, J. P., & Clark, J. E. (2005). Development of visuomotor representations for hand movement in young children. *Experimental Brain Research*, *162*(2), 155–164. https://doi.org/10.1007/s00221-004-2123-7

Cooper, L. A., & Shepard, R. N. (1975). Mental transformation in the identification of left and right hands. *Journal of Experimental Psychology: Human Perception and Performance*, *1*(1), 48–56. https://doi.org/10.1037/0096-1523.1.1.48

Cowley, J., Resnik, L., Wilken, J., Smurr Walters, L., & Gates, D. (2017). Movement quality of conventional prostheses and the DEKA Arm during everyday tasks. *Prosthetics and Orthotics International*, *41*(1), 33–40. https://doi.org/10.1177/0309364616631348

D'Alonzo, M., Clemente, F., & Cipriani, C. (2015). Vibrotactile Stimulation Promotes Embodiment of an Alien Hand in Amputees With Phantom Sensations. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *23*(3), 450–457. https://doi.org/10.1109/TNSRE.2014.2337952

Datta, D., Selvarajah, K., & Davey, N. (2004). Functional outcome of patients with proximal upper limb dee ciency-acquired and congenital. *Clinical Rehabilitation*, *18*, 172–177. https://doi.org/10.1191/0269215504cr716oa

de Heering, A., Dormal, G., Pelland, M., Lewis, T., Maurer, D., & Collignon, O. (2016). A Brief Period of Postnatal Visual Deprivation Alters the Balance between Auditory and Visual Attention. *Current Biology*, *26*(22), 3101–3105. https://doi.org/10.1016/j.cub.2016.10.014

de Lange, F. P., Helmich, R. C., & Toni, I. (2006). Posture influences motor imagery: An fMRI study. *NeuroImage*, *33*(2), 609–617. https://doi.org/10.1016/j.neuroimage.2006.07.017

de Oliveira Barata, S., Clode, D., Taylor, J., & Elias, H. (2017). *Vine Arm*. The Alternative Limb Project. http://www.thealternativelimbproject.com/project/vine/

de Vignemont, Frederique. (2010). Body schema and body image-Pros and cons. *Neuropsychologia*, *48*(3), 669–680. https://doi.org/10.1016/j.neuropsychologia.2009.09.022

de Vignemont, Frédérique. (2011). Embodiment, ownership and disownership. *Consciousness and Cognition*, *20*(1), 82–93. https://doi.org/10.1016/j.concog.2010.09.004

de Vignemont, Frédérique. (2017). Mind the body: An exploration of bodily self-awareness. In *Mind the Body: An Exploration of Bodily Self-Awareness*. Oxford University Press. https://doi.org/10.1093/oso/9780198735885.001.0001

Dempsey-Jones, H., Themistocleous, A. C., Carone, D., Ng, T. W. C., Harrar, V., & Makin, T. R. (2019). Blocking Tactile Input to One Finger Using Anaesthetic Enhances Touch Perception and Learning in Other Fingers. *Journal of Experimental Psychology: General*, *148*(4), 713–727. https://doi.org/10.1037/xge0000514.supp

Dempsey-Jones, H., Wesselink, D. B., Friedman, J., & Makin, T. R. (2019). Organized Toe Maps in Extreme Foot Users. *Cell Reports*, *28*(11), 2748-2756.e4. https://doi.org/10.1016/j.celrep.2019.08.027

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/J.NEUROIMAGE.2006.01.021

Diedrichsen, J., & Kriegeskorte, N. (2017). Representational models: A common framework for understanding encoding, pattern-component, and representational-similarity analysis. *PLOS Computational Biology*, *13*(4), e1005508. https://doi.org/10.1371/journal.pcbi.1005508

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in Psychology*, *5*(July), 1–17. https://doi.org/10.3389/fpsyg.2014.00781

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science*, *293*(5539), 2470–2473. https://doi.org/10.1126/science.1063414

Downing, P. E., & Peelen, M. V. (2016). Body selectivity in occipitotemporal cortex: Causal evidence. *Neuropsychologia*, *83*, 138–148. https://doi.org/10.1016/j.neuropsychologia.2015.05.033

Ehrsson, H. H. (2020). Multisensory processes in body ownership. In K. Sathian & Ramachandran V S (Eds.), *Multisensory Perception: From Laboratory to Clinic* (pp. 179–200). Elsevier. https://doi.org/10.1016/b978-0-12-812492-5.00008-5

Ehrsson, H. H., Rosén, B., Stockselius, A., Ragnö, C., Köhler, P., & Lundborg, G. (2008). Upper limb amputees can be induced to experience a rubber hand as their own. *Brain*, *131*(12), 3443–3452. https://doi.org/10.1093/brain/awn297

Ejaz, N., Hamada, M., & Diedrichsen, J. (2015). Hand use predicts the structure of representations in sensorimotor cortex. *Nature Neuroscience*, *18*(7), 1034–1040. https://doi.org/10.1038/nn.4038

Elliott, D., Chua, R., & Helsen, W. F. (2001). A century later: Woodworth's (1899) two-component model of goal-directed aiming. *Psychological Bulletin*, *127*(3), 342–357. https://doi.org/10.1037/0033-2909.127.3.342

Engdahl, S. M., Christie, B. P., Kelly, B., Davis, A., Chestek, C. A., & Gates, D. H. (2015). Surveying the interest of individuals with upper limb loss in novel prosthetic control techniques. *Journal of Neuroengineering and Rehabilitation*, *12*(1), 53. https://doi.org/10.1186/s12984-015-0044-2

Faisal, A. A., Selen, L. P. J., & Wolpert, D. M. (2008). Noise in the nervous system. *Nature Reviews Neuroscience*, *9*(april), 292–303. https://doi.org/10.1038/nrn2258

Fiorio, M., Tinazzi, M., & Aglioti, S. M. (2006). Selective impairment of hand mental rotation in patients with focal hand dystonia. *Brain*, *129*(1), 47–54. https://doi.org/10.1093/brain/awh630

Flor, H., Elbertt, T., Knechti, S., Wienbruchi, C., Pantevi, C., Birbaumer, N., & Taubli, W. L. B. E. (1995). *Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation*. *375*(6531), 482–484.

Flor, H., Nikolajsen, L., & Jensen, T. S. (2006). Phantom limb pain: A case of maladaptive CNS plasticity? In *Nature Reviews Neuroscience* (Vol. 7, Issue 11, pp. 873–881). https://doi.org/10.1038/nrn1991

Fossataro, C., Bruno, V., Gindri, P., Pia, L., Berti, A., & Garbarini, F. (2018). Feeling touch on the own hand restores the capacity to visually discriminate it from someone else' hand: Pathological embodiment receding in brain-damaged patients. *Cortex*, *104*, 207–219. https://doi.org/10.1016/j.cortex.2017.06.004

Fozard, J. L., Vercruyssen, M., Reynolds, S. L., Hancock, P. A., & Quilter, R. E. (1994). Age Differences and Changes in Reaction Time: The Baltimore Longitudinal Study of Aging. *Journal of Gerontology*, *49*(4), P179–P189. https://doi.org/10.1093/geronj/49.4.P179

Funk, M., & Brugger, P. (2008). Mental rotation of congenitally absent hands. *Journal of the International Neuropsychological Society*, *14*, 81–89. https://doi.org/10.1017/S1355617708080041

Gandhi, T. K., Singh, A. K., Swami, P., Ganesh, S., & Sinha, P. (2017). Emergence of categorical face perception after extended early-onset blindness. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(23), 6139–6143. https://doi.org/10.1073/pnas.1616050114

Garbarini, F., & Adenzato, M. (2004). At the root of embodied cognition: Cognitive science meets neurophysiology. *Brain and Cognition*, *56*(1), 100–106.

https://doi.org/10.1016/j.bandc.2004.06.003

Garbarini, F., Bisio, A., Biggio, M., Pia, L., & Bove, M. (2018). Motor sequence learning and intermanual transfer with a phantom limb. *Cortex*, *101*, 181–191. https://doi.org/10.1016/j.cortex.2018.01.011

Gentile, G., Guterstam, A., Brozzoli, C., & Henrik Ehrsson, H. (2013). Disintegration of multisensory signals from the real hand reduces default limb self-attribution: An fMRI study. *Journal of Neuroscience*, *33*(33), 13350–13366. https://doi.org/10.1523/JNEUROSCI.1363-13.2013

Gentilucci, M., Daprati, E., & Gangitano, M. (1998). Right-handers and left-handers have different representations of their own hand. *Cognitive Brain Research*, *6*(3), 185–192. https://doi.org/10.1016/S0926-6410(97)00034-7

Giummarra, M. J., Gibson, S. J., Georgiou-Karistianis, N., & Bradshaw, J. L. (2008). Mechanisms underlying embodiment, disembodiment and loss of embodiment. In *Neuroscience and Biobehavioral Reviews* (Vol. 32, Issue 1, pp. 143–160). Pergamon. https://doi.org/10.1016/j.neubiorev.2007.07.001

Gomez, J., Barnett, M., & Grill-Spector, K. (2019). Extensive childhood experience with Pokémon suggests eccentricity drives organization of visual cortex. *Nature Human Behaviour*, 1. https://doi.org/10.1038/s41562-019-0592-8

Gordon, J., Ghilardi, M. F., & Ghez, C. (1995). Impairments of reaching movements in patients without proprioception. I. Spatial errors. *Journal of Neurophysiology*, *73*(1), 347–360. https://doi.org/10.1152/jn.1995.73.1.347

Graczyk, E. L., Resnik, L., Schiefer, M. A., Schmitt, M. S., & Tyler, D. J. (2018). Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. *Scientific Reports*, *8*(1), 1–17. https://doi.org/10.1038/s41598-018-26952-x

Graziano, M. S. A., & Aflalo, T. N. (2007). Mapping behavioral repertoire onto the cortex. In *Neuron* (Vol. 56, Issue 2, pp. 239–251). https://doi.org/10.1016/j.neuron.2007.09.013

Graziano, M. S. A., Hu, X. T., & Gross, C. G. (1997). Visuospatial properties of ventral premotor cortex. *Journal of Neurophysiology*, *77*(5), 2268–2292. https://doi.org/10.1152/jn.1997.77.5.2268

Green, D. M., & Swets, J. A. (1966). *Signal detection theory and psychophysics.* John Wiley.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, *48*(1), 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060

Guo, X., Lin, Z., Lyu, Y., Bekrater-Bodmann, R., Flor, H., & Tong, S. (2017). The Effect of Prosthesis Use on Hand Mental Rotation After Unilateral Upper-Limb Amputation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *25*(11), 2046–2053. https://doi.org/10.1109/TNSRE.2017.2702117

Guo, X., Lyu, Y., Bekrater-Bodmann, R., Flor, H., & Tong, S. (2015). Handedness change after dominant side amputation: Evaluation from a hand laterality judgment task. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, *2015-Novem*, 8002–8005. https://doi.org/10.1109/EMBC.2015.7320249

Haak, K. V., Morland, A. B., & Engel, S. A. (2015). Plasticity, and its limits, in adult human primary visual cortex. *Multisensory Research*, *28*(3–4), 297–307. https://doi.org/10.1163/22134808-00002496

Hagura, N., Haggard, P., & Diedrichsen, J. (2017). Perceptual decisions are biased by the cost to act. *ELife*, *6*, 1–20. https://doi.org/10.7554/eLife.18422

Hahamy, A., Macdonald, S. N., van den Heiligenberg, F. M. Z., Kieliba, P., Emir, U., Malach, R., Johansen-Berg, H., Brugger, P., Culham, J. C., & Makin, T. R. (2017). Representation of Multiple Body Parts in the Missing-Hand Territory of Congenital One-Handers. *Current Biology*, *27*(9), 1350–1355. https://doi.org/10.1016/j.cub.2017.03.053

Hahamy, A., & Makin, T. R. (2018). Reorganization in cerebral and cerebellar cortices is not restricted by proximity between body-part representations. *BioRxiv*, 1–35.

Hahamy, A., & Makin, T. R. (2019). Remapping in cerebral and cerebellar cortices is not restricted by somatotopy. *Journal of Neuroscience*, *39*(47), 9328–9342. https://doi.org/10.1523/JNEUROSCI.2599-18.2019

Hahamy, A., Sotiropoulos, S. N., Henderson Slater, D., Malach, R., Johansen-Berg, H., & Makin, T. R. (2015). Normalisation of brain connectivity through compensatory behaviour, despite congenital hand absence. *ELife*, *4*. https://doi.org/10.7554/eLife.04605

Hardwick, R. M., Caspers, S., Eickhoff, S. B., & Swinnen, S. P. (2018). Neural correlates of action: Comparing meta-analyses of imagery, observation, and execution. *Neuroscience and Biobehavioral Reviews*, *94*(December 2017), 31–44. https://doi.org/10.1016/j.neubiorev.2018.08.003

Harel, A. (2016). What is special about expertise? Visual expertise reveals the interactive nature of real-world object recognition. *Neuropsychologia*, *83*, 88–99. https://doi.org/10.1016/j.neuropsychologia.2015.06.004

He, C., Peelen, M. V., Han, Z., Lin, N., Caramazza, A., & Bi, Y. (2013). Selectivity for large nonmanipulable objects in scene-selective visual cortex does not require visual experience. *NeuroImage*, *79*, 1–9. https://doi.org/10.1016/J.NEUROIMAGE.2013.04.051

Heed, T., & Röder, B. (2012). *The Neural Bases of Multisensory Processes*. Taylor & Francis.

Heimler, B., Striem-Amit, E., & Amedi, A. (2015). Origins of task-specific sensory-independent organization in the visual and auditory brain: neuroscience evidence, open questions and clinical implications. *Current Opinion in Neurobiology*, *35*, 169–177. https://doi.org/10.1016/J.CONB.2015.09.001

Hellman, R. B., Chang, E., Tanner, J., Helms Tillery, S. I., & Santos, V. J. (2015a). A robot hand testbed designed for enhancing embodiment and functional neurorehabilitation of body schema in subjects with upper limb impairment or loss. *Frontiers in Human Neuroscience*, *9*(FEB), 1–10. https://doi.org/10.3389/fnhum.2015.00026

Hellman, R. B., Chang, E., Tanner, J., Helms Tillery, S. I., & Santos, V. J. (2015b). A Robot Hand Testbed Designed for Enhancing Embodiment and Functional Neurorehabilitation of Body Schema in Subjects with Upper Limb Impairment or Loss. *Frontiers in Human Neuroscience*, *9*, 26. https://doi.org/10.3389/fnhum.2015.00026

Helmich, R. C., de Lange, F. P., Bloem, B. R., & Toni, I. (2007). Cerebral compensation during motor imagery in Parkinson's disease. *Neuropsychologia*, *45*(10), 2201–2215. https://doi.org/10.1016/j.neuropsychologia.2007.02.024

Hess, C. W., Mills, K. R., & Murray, N. M. F. (1986). Magnetic stimulation of the human brain: Facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neuroscience Letters*, *71*(2), 235–240. https://doi.org/10.1016/0304-3940(86)90565-3

Honda, T., Hirashima, M., & Nozaki, D. (2012). Adaptation to visual feedback delay influences visuomotor learning. *PLoS ONE*, *7*(5), 1–9. https://doi.org/10.1371/journal.pone.0037900

Jang, C. H., Yang, H. S., Yang, H. E., Lee, S. Y., Kwon, J. W., Yun, B. D., Choi, J. Y., Kim, S. N., & Jeong, H. W. (2011). A Survey on Activities of Daily Living and Occupations of Upper Extremity Amputees. *Annals of Rehabilitation Medicine*, *35*, 907. https://doi.org/10.5535/arm.2011.35.6.907

Jasp Team. (2020). *JASP* (0.12.2).

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156. https://doi.org/10.1016/S1361-8415(01)00036-6

Jutzeler, C. R., Freund, P., Huber, E., Curt, A., & Kramer, J. L. K. (2015). Neuropathic Pain and Functional Reorganization in the Primary Sensorimotor Cortex after Spinal Cord Injury. *Journal of Pain*, *16*(12), 1256–1267. https://doi.org/10.1016/j.jpain.2015.08.008

Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. In *Nature Reviews Neuroscience* (Vol. 12, Issue 4, pp. 231–242). Nature Publishing Group. https://doi.org/10.1038/nrn3000

Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. In *Trends in Cognitive Sciences* (Vol. 2, Issue 10, pp. 389–398). Elsevier Current Trends. https://doi.org/10.1016/S1364-6613(98)01230-3

Kerver, N., Twillert, S. Van, Maas, B., & Van Der Sluis, C. K. (2020). User-relevant factors determining prosthesis choice in persons with major unilateral upper limb defects: A meta-synthesis of qualitative literature and focus group results. *PLoS ONE*, *15*(6 June). https://doi.org/10.1371/journal.pone.0234342

Kieliba, P., Clode, D., Maimon-Mor, R. O., & Makin, T. R. (2020). Neurocognitive consequences of hand augmentation. *BioRxiv*. https://doi.org/10.1101/2020.06.16.151944

Kikkert, S., Johansen-Berg, H., Tracey, I., & Makin, T. R. (2018). Reaffirming the link between chronic phantom limb pain and maintained missing hand representation. *Cortex*, *106*, 174–184. https://doi.org/10.1016/j.cortex.2018.05.013

Kikkert, S., Kolasinski, J., Jbabdi, S., Tracey, I., Beckmann, C. F., Johansen-Berg, H., & Makin, T. R. (2016). Revealing the neural fingerprints of a missing hand. *ELife*, *5*. https://doi.org/10.7554/eLife.15292

Kikkert, S., Mezue, M., Henderson Slater, D., Johansen-Berg, H., Tracey, I., & Makin, T. R. (2017). Motor correlates of phantom limb pain. *Cortex*, *95*, 29–36. https://doi.org/10.1016/J.CORTEX.2017.07.015

Kitada, R., Yoshihara, K., Sasaki, A. T., Hashiguchi, M., Kochiyama, T., & Sadato, N. (2014). The brain network underlying the recognition of hand gestures in the blind: The supramodal role of the extrastriate body area. *Journal of Neuroscience*, *34*(30), 10096–10108. https://doi.org/10.1523/JNEUROSCI.0500-14.2014

Klein-Flügge, M. C., & Bestmann, S. (2012). Time-dependent changes in human corticospinal excitability reveal value-based competition for action during decision processing. *The Journal of Neuroscience*, *32*(24), 8373–8382. https://doi.org/10.1523/JNEUROSCI.0270-12.2012

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, *16*(8), 1412–1425.

https://doi.org/10.1162/0898929042304796

Körding, K. P., & Wolpert, D. M. (2004a). Bayesian integration in sensorimotor learning. *Nature*, *427*(6971), 244–247. https://doi.org/10.1038/nature02169

Körding, K. P., & Wolpert, D. M. (2004b). Bayesian integration in sensorimotor learning. *Nature*, *427*(6971), 244–247. https://doi.org/10.1038/nature02169

Krakauer, J. W., Ghilardi, M. F., & Ghez, C. (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nature Neuroscience*, *2*(11), 1026–1031. https://doi.org/10.1038/14826

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: An expanded neural framework for the processing of object quality. In *Trends in Cognitive Sciences* (Vol. 17, Issue 1, pp. 26–49). NIH Public Access. https://doi.org/10.1016/j.tics.2012.10.011

Kriegeskorte, N., Mur, M., Ruff, D. A., Kiani, R., Bodurka, J., Esteky, H., Tanaka, K., & Bandettini, P. A. (2008). Matching Categorical Object Representations in Inferior Temporal Cortex of Man and Monkey. *Neuron*, *60*(6), 1126–1141. https://doi.org/10.1016/J.NEURON.2008.10.043

Krubitzer, L. A., & Prescott, T. J. (2018). Special Issue: Time in the Brain The Combinatorial Creature: Cortical Phenotypes within and across Lifetimes. *Trends in Neurosciences*, *41*, 744–762. https://doi.org/10.1016/j.tins.2018.08.002

Kwak, N. S., Müller, K. R., & Lee, S. W. (2015). A lower limb exoskeleton control system based on steady state visual evoked potentials. *Journal of Neural Engineering*, *12*(5), 56009. https://doi.org/10.1088/1741-2560/12/5/056009

Lee, I. A., & Preacher, K. J. (2013). *Calculation for the test of the difference between two dependent correlations with one variable in common*. http://quantpsy.org

Leed, J. E., Chinn, L. K., & Lockman, J. J. (2019). Reaching to the Self: The Development of Infants' Ability to Localize Targets on the Body. *Psychological Science*, *30*(7), 1063–1073. https://doi.org/10.1177/0956797619850168

Limanowski, J., & Blankenburg, F. (2016). Integration of visual and proprioceptive limb position information in human posterior parietal, premotor, and extrastriate cortex. *Journal of Neuroscience*, *36*(9), 2582–2589. https://doi.org/10.1523/JNEUROSCI.3987-15.2016

Limanowski, J., Lutti, A., & Blankenburg, F. (2014). The extrastriate body area is involved in illusory limb ownership. *NeuroImage*, *86*, 514–524. https://doi.org/10.1016/j.neuroimage.2013.10.035

Lindeløv, J. K. (2011). *Calculating d', beta, c and Ad' in Python and PHP – Neuroscience, stats, and coding*. http://lindeloev.net/calculating-d-in-python-and-php/

Lingnau, A., & Downing, P. E. (2015). The lateral occipitotemporal cortex in action. *Trends in Cognitive Sciences*, *19*(5), 268–277. https://doi.org/10.1016/j.tics.2015.03.006

Longo, M. R., Sadibolova, R., & Tamè, L. (2016). Embodying prostheses – how to let the body welcome assistive devices: Comment on "The embodiment of assistive devices—from wheelchair to exoskeleton" by M. Pazzaglia and M. Molinari. *Physics of Life Reviews*, *16*, 184–185. https://doi.org/10.1016/J.PLREV.2016.01.012

Lyu, Y., Guo, X., Bekrater-Bodmann, R., Flor, H., & Tong, S. (2016). Phantom limb perception interferes with motor imagery after unilateral upper-limb amputation. *Scientific Reports*, *6*. https://doi.org/10.1038/srep21100

Lyu, Y., Guo, X., Bekrater-Bodmann, R., Flor, H., & Tong, S. (2017). An event-related potential study on the time course of mental rotation in upper-limb amputees. *Clinical Neurophysiology*, *128*(5), 744–750. https://doi.org/10.1016/j.clinph.2017.02.008

Macdonald, S., van den Heiligenberg, F., Makin, T., & Culham, J. (2017). Videos are more effective than pictures at localizing tool- and hand-selective activation in fMRI. *Journal of Vision*, *17*(10), 991. https://doi.org/10.1167/17.10.991

Mahon, B. Z., & Caramazza, A. (2011). What drives the organization of object knowledge in the brain? The distributed domain-specific hypothesis. *Trends in Cognitive Sciences*, *15*(3), 97–103. https://doi.org/10.1016/j.tics.2011.01.004

Maimon-Mor, R. O., Johansen-Berg, H., & Makin, T. R. (2017). Peri-hand space representation in the absence of a hand – Evidence from congenital one-handers. *Cortex*, *95*, 169–171. https://doi.org/10.1016/j.cortex.2017.08.016

Maimon-Mor, R. O., & Makin, T. R. (2020). Is an artificial limb embodied as a hand? Brain decoding in prosthetic limb users. *PLOS Biology*, *18*(6), e3000729. https://doi.org/10.1371/journal.pbio.3000729

Maimon-Mor, R. O., Obasi, E., Lu, J., Odeh, N., Kirker, S., MacSweeney, M., Goldin-Meadow, S., & Makin, T. R. (2020a). Talking with Your (Artificial) Hands: Communicative Hand Gestures as an Implicit Measure of Embodiment. *IScience*, *23*(11). https://doi.org/10.1016/j.isci.2020.101650

Maimon-Mor, R. O., Obasi, E., Lu, J., Odeh, N., Kirker, S., MacSweeney, M., Goldin-Meadow, S., & Makin, T. R. (2020b). Communicative hand gestures as an implicit measure of artificial limb embodiment and daily usage. *MedRxiv*, 2020.03.11.20033928. https://doi.org/10.1101/2020.03.11.20033928

Maimon-Mor, R. O., Schone, H. R., Moran, R., Brugger, P., & Makin, T. R. (2020). Motor control drives visual bodily judgements. *Cognition*, *196*. https://doi.org/10.1016/j.cognition.2019.104120

Makin, T. R., & Bensmaia, S. J. (2017). Stability of Sensory Topographies in Adult Cortex. In *Trends in Cognitive Sciences* (Vol. 21, Issue 3, pp. 195–204). NIH Public Access. https://doi.org/10.1016/j.tics.2017.01.002

Makin, T. R., Cramer, A. O., Scholz, J., Hahamy, A., Henderson Slater, D., Tracey, I., & Johansen-Berg, H. (2013). Deprivation-related and use-dependent plasticity go hand in hand. *ELife*, *2013*, 1–15. https://doi.org/10.7554/eLife.01273.01273

Makin, T. R., de Vignemont, F., & Faisal, A. A. (2017). Neurocognitive barriers to the embodiment of technology. *Nature Biomedical Engineering*, *1*(1), 0014. https://doi.org/10.1038/s41551-016-0014

Makin, T. R., de Vignemont, F., & Micera, S. (2020). Soft Embodiment for Engineering Artificial Limbs. *Trends in Cognitive Sciences*, *0*(0). https://doi.org/10.1016/j.tics.2020.09.008

Makin, T. R., Holmes, N. P., Brozzoli, C., & Farnè, A. (2012). Keeping the world at hand: rapid visuomotor processing for hand–object interactions. *Experimental Brain Research*, *219*(4), 421–428. https://doi.org/10.1007/s00221-012-3089-5

Makin, T. R., Holmes, N. P., & Ehrsson, H. H. (2008). On the other hand: Dummy hands and peripersonal space. *Behavioural Brain Research*, *191*(1), 1–10. https://doi.org/10.1016/j.bbr.2008.02.041

Makin, T. R., & London Plasticity Lab. (2020). Phantom Limbs and Brain Plasticity in Amputees. In *Oxford Research Encyclopedia of Neuroscience*. Oxford University Press.

https://doi.org/10.1093/acrefore/9780190264086.013.50

Makin, T. R., & Orban de Xivry, J. J. (2019). Ten common statistical mistakes to watch out for when writing or reviewing a manuscript. *ELife*, *8*(e48175), 1–13. https://doi.org/10.7554/eLife.48175

Makin, T. R., Scholz, J., Filippini, N., Slater, D. H., Tracey, I., Johansen-berg, H., & Henderson Slater, D. (2013). Phantom pain is associated with preserved structure and function in the former hand area. *Nature Communications*, *4*, 1570. https://doi.org/10.1038/ncomms2571

Makin, T. R., Scholz, J., Henderson Slater, D., Johansen-Berg, H., & Tracey, I. (2015). Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain*, *138*(8), 2140–2146. https://doi.org/10.1093/brain/awv161

Makin, T. R., Wilf, M., Schwartz, I., & Zohary, E. (2010). Amputees "neglect" the space near their missing hand. *Psychological Science*, *21*(1), 55–57. https://doi.org/10.1177/0956797609354739

Marasco, P. D., Hebert, J. S., Sensinger, J. W., Shell, C. E., Schofield, J. S., Thumser, Z. C., Nataraj, R., Beckler, D. T., Dawson, M. R., Blustein, D. H., Gill, S., Mensh, B. D., Granja-Vazquez, R., Newcomb, M. D., Carey, J. P., & Orzell, B. M. (2018). Illusory movement perception improves motor control for prosthetic hands. *Science Translational Medicine*, *10*(432), 1–13. https://doi.org/10.1126/scitranslmed.aao6990

Marasco, P. D., Kim, K., Colgate, J. E., Peshkin, M. A., & Kuiken, T. A. (2011). Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain*, *134*(3), 747–758. https://doi.org/10.1093/brain/awq361

Martens, F., Bulthé, J., van Vliet, C., & Op de Beeck, H. (2018). Domain-general and domain-specific neural changes underlying visual expertise. *NeuroImage*, *169*, 80–93. https://doi.org/10.1016/J.NEUROIMAGE.2017.12.013

Martinaud, O., Besharati, S., Jenkinson, P. M., & Fotopoulou, A. (2017). Ownership illusions in patients with body delusions: Different neural profiles of visual capture and disownership. *Cortex*, *87*, 174–185. https://doi.org/10.1016/j.cortex.2016.09.025

McDonnell, P. M., Scott, R. N., Dickison, J., Anne Theriault, R., & Wood, B. (1989). Do artificial limbs become part of the user? New evidence. *Journal of Rehabilitation Research and Development*, *26*(2), 17–24.

McGugin, R. W., Van Gulick, A. E., Tamber-Rosenau, B. J., Ross, D. A., & Gauthier, I. (2015). Expertise Effects in Face-Selective Areas are Robust to Clutter and Diverted Attention, but not to Competition. *Cerebral Cortex*, *25*, 26610–2622. https://doi.org/10.1093/cercor/bhu060

Metta, G., Sandini, G., Vernon, D., Natale, L., & Nori, F. (2008). The iCub humanoid robot: an open platform for research in embodied cognition. *Proceedings of the 8th Workshop on Performance Metrics for Intelligent Systems - PerMIS '08*, *January*, 50. https://doi.org/10.1145/1774674.1774683

Mezue, M., & Makin, T. (2017). Immutable Body Representations: Lessons from Phantoms in Amputees. In *The Subject's Matter: Self-Consciousness and the Body*. https://doi.org/10.7551/mitpress/10462.003.0004

Miller, L. E., Montroni, L., Koun, E., Salemme, R., Hayward, V., & Farnè, A. (2018). Sensing with tools extends somatosensory processing beyond the body. *Nature*, *561*(7722), 239–242. https://doi.org/10.1038/s41586-018-0460-0

Miyashita-Lin, E. M., Hevner, R., Wassarman, K. M., Martinez, S., & Rubenstein, J. L. R. (1999). Early neocortical regionalization in the absence of thalamic innervation. *Science*, *285*(5429), 906–909. https://doi.org/10.1126/science.285.5429.906

Moran, R., Zehetleitner, M., Liesefeld, H. R., Müller, H. J., & Usher, M. (2016). Serial vs. parallel models of attention in visual search: accounting for benchmark RT-distributions. *Psychonomic Bulletin & Review*, *23*(5), 1300–1315. https://doi.org/10.3758/s13423-015-0978-1

Morey, R. D., & Rouder, J. N. (2015). *BayesFactor* (0.9.10-2).

Moseley, G. L. (2004). Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology*, *62*(12), 2182–2186. https://doi.org/10.1212/01.WNL.0000130156.05828.43

Mulvey, M. R., Fawkner, H. J., Radford, H. E., & Johnson, M. I. (2012). Perceptual Embodiment of Prosthetic Limbs by Transcutaneous Electrical Nerve Stimulation. *Neuromodulation: Technology at the Neural Interface*, *15*(1), 42–47. https://doi.org/10.1111/j.1525-1403.2011.00408.x

Murray, C. D. (2008). Embodiment and Prosthetics. In P. Gallagher, D. Desmond, & M. MacLachlan (Eds.), *Psychoprosthetics: State of the Knowledge* (pp. 119–129). Springer London. https://doi.org/10.1007/978-1-84628-980-4_9

Myers, A., & Sowden, P. T. (2008). Your hand or mine? The extrastriate body area. *NeuroImage*, *42*(4), 1669–1677. https://doi.org/10.1016/j.neuroimage.2008.05.045

Nico, D., Daprati, E., Rigal, F., Parsons, L., & Sirigu, A. (2004). Left and right hand recognition in upper limb amputees. *Brain*, *127*(1), 120–132. https://doi.org/10.1093/brain/awh006

Nili, H., Wingfield, C., Walther, A., Su, L., Marslen-Wilson, W., & Kriegeskorte, N. (2014). A Toolbox for Representational Similarity Analysis. *PLoS Computational Biology*, *10*(4). https://doi.org/10.1371/journal.pcbi.1003553

Oberg, K. C. (2018). Classification of congenital upper limb anomalies: towards improved communication, diagnosis, and discovery. *Journal of Hand Surgery*, *44*(1), 4–14. https://doi.org/10.1177/1753193418801280

Oliveira, F. T. P., Diedrichsen, J., Verstynen, T., Duque, J., & Ivry, R. B. (2010). Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(41), 17751–17756. https://doi.org/10.1073/pnas.1006223107

Olivier, I., Hay, L., Bard, C., & Fleury, M. (2007). Age-related differences in the reaching and grasping coordination in children: Unimanual and bimanual tasks. *Experimental Brain Research*, *179*(1), 17–27. https://doi.org/10.1007/s00221-006-0762-6

Op de Beeck, H. P., Pillet, I., & Ritchie, J. B. (2019). Factors Determining Where Category-Selective Areas Emerge in Visual Cortex. In *Trends in Cognitive Sciences* (Vol. 23, Issue 9, pp. 784–797). Elsevier Ltd. https://doi.org/10.1016/j.tics.2019.06.006

Orlov, T., Makin, T. R., & Zohary, E. (2010). Topographic Representation of the Human Body in the Occipitotemporal Cortex. *Neuron*, *68*(3), 586–600. https://doi.org/10.1016/j.neuron.2010.09.032

Orlov, T., Porat, Y., Makin, T. R., & Zohary, E. (2014). Hands in motion: An upper-limb-selective area in the occipitotemporal cortex shows sensitivity to viewed hand kinematics. *Journal of Neuroscience*, *34*(14), 4882–4895. https://doi.org/10.1523/JNEUROSCI.3352-13.2014

Østlie, K., Lesjø, I. M., Franklin, R. J., Garfelt, B., Skjeldal, O. H., & Magnus, P. (2012). Prosthesis rejection in acquired major upper-limb amputees: a population-based survey. *Disability and Rehabilitation: Assistive Technology*, *7*(4), 294–303.

https://doi.org/10.3109/17483107.2011.635405

Østlie, K., Magnus, P., Skjeldal, O. H., Garfelt, B., & Tambs, K. (2011). Mental health and satisfaction with life among upper limb amputees: a Norwegian population-based survey comparing adult acquired major upper limb amputees with a control group. *Disability and Rehabilitation*, *33*(17–18), 1594–1607. https://doi.org/10.3109/09638288.2010.540293

Parsons, L. M. (1987). Imagined spatial transformations of one's hands and feet. *Cognitive Psychology*, *19*(2), 178–241. https://doi.org/10.1016/0010-0285(87)90011-9

Parsons, L. M. (1994). Temporal and Kinematic Properties of Motor Behavior Reflected in Mentally Simulated Action. *Journal of Experimental Psychology*, *20*(4), 709–730.

Patterson, J. R., Brown, L. E., Wagstaff, D. A., & Sainburg, R. L. (2017). Limb position drift results from misalignment of proprioceptive and visual maps. *Neuroscience*, *346*, 382–394. https://doi.org/10.1016/j.neuroscience.2017.01.040

Pazzaglia, M., & Molinari, M. (2016). The embodiment of assistive devices-from wheelchair to exoskeleton. In *Physics of Life Reviews* (Vol. 16, pp. 163–175). Elsevier. https://doi.org/10.1016/j.plrev.2015.11.006

Peelen, M. V., & Downing, P. E. (2007). The neural basis of visual body perception. *Nature Reviews Neuroscience*, *8*(8), 636–648. https://doi.org/10.1038/nrn2195

Peelen, M. V, Bracci, S., Lu, X., He, C., Caramazza, A., & Bi, Y. (2013). *Tool Selectivity in Left Occipitotemporal Cortex Develops without Vision*. https://doi.org/10.1162/jocn_a_00411

Penaloza, C. I., & Nishio, S. (2018). BMI control of a third arm for multitasking. *Science Robotics*, *3*(20), eaat1228. https://doi.org/10.1126/scirobotics.aat1228

Penhune, V. B. (2011). Sensitive periods in human development: Evidence from musical training. In *Cortex* (Vol. 47, Issue 9, pp. 1126–1137). Elsevier. https://doi.org/10.1016/j.cortex.2011.05.010

Petrini, F. M., Valle, G., Strauss, I., Granata, G., Di Iorio, R., D'Anna, E., Čvančara, P., Mueller, M., Carpaneto, J., Clemente, F., Controzzi, M., Bisoni, L., Carboni, C., Barbaro, M., Iodice, F., Andreu, D., Hiairrassary, A., Divoux, J. L., Cipriani, C., … Micera, S. (2019). Six-Month Assessment of a Hand Prosthesis with Intraneural Tactile Feedback. *Annals of Neurology*, *85*(1), 137–154. https://doi.org/10.1002/ana.25384

Philip, B. A., Buckon, C., Sienko, S., Aiona, M., Ross, S., & Frey, S. H. (2015). Maturation and experience in action representation: Bilateral deficits in unilateral congenital amelia. *Neuropsychologia*, *75*, 420–430. https://doi.org/10.1016/j.neuropsychologia.2015.05.018

Philip, B. A., & Frey, S. H. (2011). Preserved grip selection planning in chronic unilateral upper extremity amputees. *Exp Brain Res*, *214*, 437–452. https://doi.org/10.1007/s00221-011-2842-5

Philip, B. A., & Frey, S. H. (2014). Compensatory Changes Accompanying Chronic Forced Use of the Nondominant Hand by Unilateral Amputees. *Journal of Neuroscience*, *34*(10), 3622–3631. https://doi.org/10.1523/JNEUROSCI.3770-13.2014

Piazza, C., Grioli, G., Catalano, M. G., & Bicchi, A. (2019). A Century of Robotic Hands. *Robotics, and Autonomous Systems Annu. Rev. Control Robot. Auton. Syst. 2019*, *22*, 1–32. https://doi.org/10.1146/annurev-control-060117

Przybyla, A., Coelho, C. J., Akpinar, S., Kirazci, S., & Sainburg, R. L. (2013). Sensorimotor performance asymmetries predict hand selection. *Neuroscience*, *228*, 349–360. https://doi.org/10.1016/j.neuroscience.2012.10.046

Raffin, E., Giraux, P., & Reilly, K. T. (2012). The moving phantom: Motor execution or motor imagery? *Cortex*, *48*(6), 746–757. https://doi.org/10.1016/j.cortex.2011.02.003

Raffin, E., Mattout, J., Reilly, K. T., & Giraux, P. (2012). Disentangling motor execution from motor imagery with the phantom limb. *Brain*, *135*(2).

Raffin, E., Richard, N., Giraux, P., & Reilly, K. T. (2016). Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb. *NeuroImage*, *130*, 134–144. https://doi.org/10.1016/j.neuroimage.2016.01.063

Raichle, K. A., Hanley, M. A., Molton, I., Kadel, N. J., Campbell, K., Phelps, E., Ehde, D., & Smith, D. G. (2008). Prosthesis use in persons with lower- and upper-limb amputation. *Journal of Rehabilitation Research & Development*, *45*(7), 961–972. https://doi.org/10.1055/s-0029-1237430.Imprinting

Ratcliff, R., & Mckoon, G. (2008). The Diffusion Decision Model: Theory and Data for Two-Choice Decision Tasks. *Neural Computation*, *20*, 873–922.

Reddy, L., & Kanwisher, N. (2006). Coding of visual objects in the ventral stream. *Current Opinion in Neurobiology*, *16*(4), 408–414. https://doi.org/10.1016/J.CONB.2006.06.004

Reilly, K. T., Mercier, C., Schieber, M. H., & Sirigu, A. (2006). Persistent hand motor commands in the amputees' brain. *Brain*, *129*(8), 2211–2223. https://doi.org/10.1093/brain/awl154

Reilly, K. T., & Sirigu, A. (2008). The motor cortex and its role in phantom limb phenomena. In *Neuroscientist* (Vol. 14, Issue 2, pp. 195–202). Sage PublicationsSage CA: Los Angeles, CA. https://doi.org/10.1177/1073858407309466

Reilly, K. T., & Sirigu, A. (2011). Motor cortex representation of the upper-limb in individuals born without a hand. *PLoS ONE*, *6*(4). https://doi.org/10.1371/journal.pone.0018100

Rekant, J. S., Fisher, L. E., Boninger, M. L., Gaunt, R. A., & Collinger, J. L. (2020). Amputee, clinician, and regulator perspectives on current and prospective upper extremity prosthetic technologies. *MedRxiv*. https://doi.org/10.1101/2020.08.07.20170209

Resnik, L., Klinger, S. L., & Etter, K. (2014). The DEKA Arm: Its features, functionality, and evolution during the veterans affairs study to optimize the DEKA Arm. *Prosthetics and Orthotics International*, *38*(6), 492–504. https://doi.org/10.1177/0309364613506913

Rognini, G., Petrini, F. M., Raspopovic, S., Valle, G., Granata, G., Strauss, I., Solcà, M., Bello-Ruiz, J., Herbelin, B., Mange, R., D'Anna, E., Di Iorio, R., Di Pino, G., Andreu, D., Guiraud, D., Stieglitz, T., Rossini, P. M., Serino, A., Micera, S., & Blanke, O. (2019). Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. In *Journal of Neurology, Neurosurgery and Psychiatry* (Vol. 90, Issue 7, pp. 833–836). BMJ Publishing Group Ltd. https://doi.org/10.1136/jnnp-2018-318570

Rosén, B., Ehrsson, H. H., Antfolk, C., Cipriani, C., Sebelius, F., & Lundborg, G. (2009). Referral of sensation to an advanced humanoid robotic hand prosthesis. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, *43*(5), 260–266. https://doi.org/10.3109/02844310903113107

Ross, D. A., Tamber-Rosenau, B. J., Palmeri, T. J., Zhang, J., Xu, Y., & Gauthier, I. (2018). High-resolution Functional Magnetic Resonance Imaging Reveals Configural Processing of Cars in Right Anterior Fusiform Face Area of Car Experts. *Journal of Cognitive Neuroscience*, *30*(7), 973–984. https://doi.org/10.1162/jocn_a_01256

Rouder, J. N., Engelhardt, C. R., McCabe, S., & Morey, R. D. (2016). Model comparison in ANOVA. *Psychonomic Bulletin and Review*, *23*(6), 1779–1786. https://doi.org/10.3758/s13423-016-1026-5

Rouder, J. N., Morey, R. D., Speckman, P. L., & Province, J. M. (2012). Default Bayes factors for ANOVA designs. *Journal of Mathematical Psychology*, *56*(5), 356–374. https://doi.org/10.1016/j.jmp.2012.08.001

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. In *Psychonomic Bulletin and Review* (Vol. 16, Issue 2, pp. 225–237). Springer. https://doi.org/10.3758/PBR.16.2.225

Rubenstein, J. L. R., Anderson, S., Shi, L., Miyashita-Lin, E., Bulfone, A., & Hevner, R. (1999). Genetic control of cortical regionalization and connectivity. *Cerebral Cortex*, *9*(6), 524–532. https://doi.org/10.1093/cercor/9.6.524

Sainburg, R. L., Lateiner, J. E., Latash, M. L., & Bagesteiro, L. B. (2003). Effects of altering initial position on movement direction and extent. *Journal of Neurophysiology*, *89*(1), 401–415. https://doi.org/10.1152/jn.00243.2002

Sarlegna, F. R., & Sainburg, R. L. (2009). The roles of vision and proprioception in the planning of reaching movements. *Advances in Experimental Medicine and Biology*, *629*, 317–335. https://doi.org/10.1007/978-0-387-77064-2_16

Saunders, J. A. (2004). Visual Feedback Control of Hand Movements. *Journal of Neuroscience*, *24*(13), 3223–3234. https://doi.org/10.1523/JNEUROSCI.4319-03.2004

Saxe, R., Jamal, N., & Powell, L. (2006). My body or yours? The effect of visual perspective on cortical body representations. *Cerebral Cortex*, *16*(2), 178–182. https://doi.org/10.1093/cercor/bhi095

Scheperjans, F., Eickhoff, S. B., Hömke, L., Mohlberg, H., Hermann, K., Amunts, K., & Zilles, K. (2008). Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. *Cerebral Cortex*, *18*(9), 2141–2157. https://doi.org/10.1093/cercor/bhm241

Schmalzl, L., Kalckert, A., Ragnö, C., & Ehrsson, H. H. (2014). Neural correlates of the rubber hand illusion in amputees: A report of two cases. *Neurocase*, *20*(4), 407–420. https://doi.org/10.1080/13554794.2013.791861

Schneiberg, S., Sveistrup, H., Mcfadyen, B., Mckinley, P., & Levin, M. F. (2002). The development of coordination for reach-to-grasp movements in children. *Exp Brain Res*, *146*, 142–154. https://doi.org/10.1007/s00221-002-1156-z

Schwoebel, J., & Coslett, H. B. (2005). Evidence for Multiple, Distinct Representations of the Human Body. *Journal of Cognitive Neuroscience*, *17–4*, 543–553.

Scott, S. H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews Neuroscience*, *5*(7), 532–546. https://doi.org/10.1038/nrn1427

Seger, C. A., & Miller, E. K. (2010). *Category Learning in the Brain*. https://doi.org/10.1146/annurev.neuro.051508.135546

Sekiyama, K. (1982). Kinesthetic aspects of mental representations in the identification of left and right hands. *Perception & Psychophysics*, *32*(2), 89–95. https://doi.org/10.3758/BF03204268

Shapiro, L. (2019). *Embodied Cognition*. Routledge. https://doi.org/10.4324/9781315180380

Simon-Martinez, C., Lopes Dos Santos, G., Jaspers, E., Vanderschueren, R., Mailleux, L., Klingels, K., Ortibus, E., Desloovere, K., & Feys, H. (2018). *Age-related changes in upper limb motion during typical development*. https://doi.org/10.1371/journal.pone.0198524

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Soekadar, S. R., Witkowski, M., Gómez, C., Opisso, E., Medina, J., Cortese, M., Cempini, M., Carrozza, M. C., Cohen, L. G., Birbaumer, N., & Vitiello, N. (2016). Hybrid EEG/EOG-based brain/neural hand exoskeleton restores fully independent daily living activities after quadriplegia. *Science Robotics*, *1*(1), eaag3296. https://doi.org/10.1126/scirobotics.aag3296

Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers*, *31*(1), 137–149. https://doi.org/10.3758/BF03207704

Stankevicius, A., Wallwork, S. B., Summers, S. J., Hordacre, B., & Stanton, T. R. (2020). Prevalence and incidence of phantom limb pain, phantom limb sensations and telescoping in amputees: A systematic rapid review. *European Journal of Pain*, ejp.1657. https://doi.org/10.1002/ejp.1657

Stark-Inbar, A., Raza, M., Taylor, J. A., & Ivry, R. B. (2017). Individual differences in implicit motor learning: task specificity in sensorimotor adaptation and sequence learning. *Journal of Neurophysiology*, *117*(1), 412–428. https://doi.org/10.1152/jn.01141.2015

Stoeckel, M. C., Seitz, R. J., & Buetefisch, C. M. (2009a). Congenitally altered motor experience alters somatotopic organization of human primary motor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(7), 2395–2400. https://doi.org/10.1073/pnas.0803733106

Stoeckel, M. C., Seitz, R. J., & Buetefisch, C. M. (2009b). Congenitally altered motor experience alters somatotopic organization of human primary motor cortex. *National Institutes of Mental Health*, *106*(7), 2395–2400. www.pnas.org/cgi/content/full/

Striem-Amit, E., & Amedi, A. (2014). Visual Cortex Extrastriate Body-Selective Area Activation in Congenitally Blind People "“Seeing”" by Using Sounds. *Current Biology*, *24*, 687–692. https://ac.els-cdn.com/S0960982214001481/1-s2.0-S0960982214001481-main.pdf?_tid=39dd406d-4117-4ece-9199-65b6f36d0faf&acdnat=1548263699_e548b32c53c2e96f97737cd75555fcbc

Striem-Amit, E., Dakwar, O., Reich, L., & Amedi, A. (2012). The large-Scale Organization of "“Visual”" Streams Emerges Without Visual Experience. *Cerebral Cortex*, *22*, 1698–1709. https://doi.org/10.1093/cercor/bhr253

Striem-Amit, E., Vannuscorps, G., & Caramazza, A. (2017). Sensorimotor-independent development of hands and tools selectivity in the visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(18), 4787–4792. https://doi.org/10.1073/pnas.1620289114

Striem-Amit, E., Vannuscorps, G., & Caramazza, A. (2018a). Plasticity based on compensatory effector use in the association but not primary sensorimotor cortex of people born without hands. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(30), 7801–7806. https://doi.org/10.1073/pnas.1803926115

Striem-Amit, E., Vannuscorps, G., & Caramazza, A. (2018b). Plasticity based on compensatory effector use in the association but not primary sensorimotor cortex of people born without hands. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(30), 7801–7806. https://doi.org/10.1073/pnas.1803926115

Sur, M., & Rubenstein, J. L. R. (2005). Patterning and plasticity of the cerebral cortex. In *Science* (Vol. 310, Issue 5749, pp. 805–810). American Association for the Advancement of Science. https://doi.org/10.1126/science.1112070

Sveistrup, H., Schneiberg, S., McKinley, P. A., McFadyen, B. J., & Levin, M. F. (2008). Head, arm and trunk coordination during reaching in children. *Experimental Brain Research*, *188*(2), 237–247. https://doi.org/10.1007/s00221-008-1357-1

Takeda, K., Shimoda, N., Sato, Y., Ogano, M., & Kato, H. (2010). Reaction time differences between left- and right-handers during mental rotation of hand pictures. *Laterality*, *15*(4), 415–425. https://doi.org/10.1080/13576500902938105

Tal, Z., Geva, R., & Amedi, A. (2016). The origins of metamodality in visual object area LO: Bodily topographical biases and increased functional connectivity to S1. *NeuroImage*, *127*, 363–375. https://doi.org/10.1016/j.neuroimage.2015.11.058

Tan, D. W., Schiefer, M. A., Keith, M. W., Anderson, J. R., Tyler, J., & Tyler, D. J. (2014). A neural interface provides long-term stable natural touch perception. *Science Translational Medicine*, *6*(257), 257ra138. https://doi.org/10.1126/scitranslmed.3008669

Tsakiris, M. (2010). My body in the brain: A neurocognitive model of body-ownership. *Neuropsychologia*, *48*(3), 703–712. https://doi.org/10.1016/j.neuropsychologia.2009.09.034

Tsao, D. Y., & Livingstone, M. S. (2008). Mechanisms of Face Perception. *Annual Review of Neuroscience*, *31*(1), 411–437. https://doi.org/10.1146/annurev.neuro.30.051606.094238

Tyler, D. J. (2015). Neural interfaces for somatosensory feedback: bringing life to a prosthesis. *Current Opinion in Neurology*, *28*(6), 574–581. https://doi.org/10.1097/WCO.0000000000000266

Uğurbil, K., Xu, J., Auerbach, E. J., Moeller, S., Vu, A. T., Duarte-Carvajalino, J. M., Lenglet, C., Wu, X., Schmitter, S., Van de Moortele, P. F., Strupp, J., Sapiro, G., De Martino, F., Wang, D., Harel, N., Garwood, M., Chen, L., Feinberg, D. A., Smith, S. M., … Yacoub, E. (2013). Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project. *NeuroImage*, *80*, 80–104. https://doi.org/10.1016/J.NEUROIMAGE.2013.05.012

Uswatte, G., Taub, E., Morris, D., Light, K., & Thompson, P. A. (2006). The Motor Activity Log-28: assessing daily use of the hemiparetic arm after stroke. *Neurology*, *67*(7), 1189–1194. https://doi.org/10.1212/01.wnl.0000238164.90657.c2

Valle, G., Mazzoni, A., Iberite, F., D'Anna, E., Strauss, I., Granata, G., Controzzi, M., Clemente, F., Rognini, G., Cipriani, C., Stieglitz, T., Petrini, F. M., Rossini, P. M., & Micera, S. (2018). Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis. *Neuron*, *100*(1), 37-45.e7. https://doi.org/10.1016/J.NEURON.2018.08.033

Van Beers, R. J., Haggard, P., & Wolpert, D. M. (2004). The Role of Execution Noise in Movement Variability. *Journal of Neurophysiology*, *91*(2), 1050–1063. https://doi.org/10.1152/jn.00652.2003

Van Beers, R. J., Sittig, A. C., & Denier Van Der Gon, J. J. (1999). Integration of proprioceptive and visual position-information: An experimentally supported model. *Journal of Neurophysiology*, *81*(3), 1355–1364. https://doi.org/10.1152/jn.1999.81.3.1355

Van Den Heiligenberg, F. M. Z., Orlov, T., MacDonald, S. N., Duff, E. P., Henderson Slater, D., Beckmann, C. F., Johansen-Berg, H., Culham, J. C., & Makin, T. R. (2018). Artificial limb representation in amputees. *Brain*, *141*(5), 1422–1433. https://doi.org/10.1093/brain/awy054

van den Heiligenberg, F. M. Z., Yeung, N., Brugger, P., Culham, J. C., & Makin, T. R. (2017).

Adaptable Categorization of Hands and Tools in Prosthesis Users. *Psychological Science*, *28*(3), 395–398. https://doi.org/10.1177/0956797616685869

Vannuscorps, G., & Caramazza, A. (2015). Typical biomechanical bias in the perception of congenitally absent hands. *Cortex*, *67*, 147–150. https://doi.org/10.1016/j.cortex.2015.02.015

Vannuscorps, G., & Caramazza, A. (2016). Typical action perception and interpretation without motor simulation. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(1), 86–91. https://doi.org/10.1073/pnas.1516978112

Vannuscorps, G., Pillon, A., & Andres, M. (2012). Effect of biomechanical constraints in the hand laterality judgment task: where does it come from? *Frontiers in Human Neuroscience*, *6*, 1–9. https://doi.org/10.3389/fnhum.2012.00299

von Hofsten, C. (1980). Predictive reaching for moving objects by human infants. *Journal of Experimental Child Psychology*, *30*(3), 369–382. https://doi.org/10.1016/0022-0965(80)90043-0

Vujaklija, I., Farina, D., & Aszmann, O. C. (2016). New developments in prosthetic arm systems. In *Orthopedic Research and Reviews* (Vol. 8, pp. 31–39). https://doi.org/10.2147/ORR.S71468

Walsh, E., Long, C., & Haggard, P. (2015). Voluntary control of a phantom limb. *Neuropsychologia*, *75*, 341–348. https://doi.org/10.1016/j.neuropsychologia.2015.06.032

Walther, A., Nili, H., Ejaz, N., Alink, A., Kriegeskorte, N., & Diedrichsen, J. (2016). Reliability of dissimilarity measures for multi-voxel pattern analysis. *NeuroImage*, *137*, 188–200. https://doi.org/10.1016/J.NEUROIMAGE.2015.12.012

Walton, K. D., Lieberman, D., Llinás, A., Begin, M., & Llinás, R. R. (1992). Identification of a critical period for motor development in neonatal rats. *Neuroscience*, *51*(4), 763–767. https://doi.org/10.1016/0306-4522(92)90517-6

Wesselink, D. B., Heiligenberg, F. M. Van Den, Ejaz, N., Dempsey-Jones, H., Cardinali, L., Tarall-Jozwiak, A., Diedrichsen, J., & Makin, T. R. (2019). Obtaining and maintaining cortical hand representation as evidenced from acquired and congenital handlessness. *ELife*, *8*(e37227), 1–19. https://doi.org/10.7554/eLife.37227

Wesselink, D. B., & Maimon-Mor, R. O. (2018). *RSA toolbox extension for FSL* (1.1).

Wetzels, R., Matzke, D., Lee, M. D., Rouder, J. N., Iverson, G. J., & Wagenmakers, E. J. (2011). Statistical evidence in experimental psychology: An empirical comparison using 855 t tests. *Perspectives on Psychological Science*, *6*(3), 291–298. https://doi.org/10.1177/1745691611406923

Wilson, M. (2002). Six Views of Embodied Cognition. *Cognition*, *9*(4), 1–19.

Wolpert, D. M. (1997). Computational approaches to motor control. *Trends in Cognitive Sciences*, *1*(6), 209–216.

Wolpert, D. M., Diedrichsen, J., & Flanagan, J. R. (2011). Principles of sensorimotor learning. *Nature Reviews Neuroscience*, *12*(12), 739–751. https://doi.org/10.1038/nrn3112

Wolpert, D. M., Ghahramani, Z., & Jordan, M. I. (1995). An Internal Model for Sensorimotor Integration. *Science*, *269*(29), 1880–1882. http://links.jstor.org/sici?sici=0036-8075%2819950929%293%3A269%3A5232%3C1880%3AAIMFSI%3E2.0.CO%3B2-Q

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*(6), 1370–1386.

https://doi.org/10.1006/nimg.2001.0931

Wu, F. Y., & Asada, H. H. (2015). “Hold-and-Manipulate” with a Single Hand Being Assisted by Wearable Extra Fingers. *Robotics and Automation (ICRA), 2015 IEEE International Conference On.*, 6205–6212.

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. https://doi.org/10.1038/nmeth.1635

Yu, X. J., He, H. J., Zhang, Q. W., Zhao, F., Zee, C. S., Zhang, S. Z., & Gong, X. Y. (2014). Somatotopic reorganization of hand representation in bilateral arm amputees with or without special foot movement skill. *Brain Research*, *1546*, 9–17. https://doi.org/10.1016/J.BRAINRES.2013.12.025

Zeiler, S. R., & Krakauer, J. W. (2013). The interaction between training and plasticity in the poststroke brain. *Current Opinion in Neurology*, *26*(6), 609–616. https://doi.org/10.1097/WCO.0000000000000025

Zoia, S., Bulgheroni, M., Acus, A., & Skabar, A. (2007). *Accessible gaming View project Rewire-Rehabilitative Wayout In Responsive home Environments View project*. https://doi.org/10.1007/s00221-006-0607-3

Appendices

5.1 Supplementary Materials

5.1.1 Supplementary Materials Chapter 1

Hand Laterality Judgement: Stimuli Difficulty Split

To assess hand posture image difficulty, a separate group of 13 able-bodied two-handed controls (mean age ± s.e.m. = 42.9 ± 3, 4 left-hand dominant; 3 females) performed the hand laterality judgment task described in the main text with the only exception of completing a single experimental block instead of two. In other words, each hand posture image was presented only once. RTs where averaged across hands (left- and right-hand image of the same posture) and participants. Difficulty was categorised using a median split, with images below the overall median (1.46s) labelled as ‘easy’, and above as ‘hard’ (see Figure S1 for all stimuli divided to easy and hard postures).

Control Task: Category Naming

Data used here was taken from a previously published study with the same participants (van den Heiligenberg et al., 2017). In brief, participants performed a visual priming task in which they verbally categorized target images of hands and tools. The experimental set up was identical to that used in the present study, and data was collected during the same session. Trials included in our analysis are the 40 baseline trials in which a scrambled image (neutral prime) was followed by a target stimulus of a hand or a tool, presented for 32ms (stimulus onset asynchrony = 600ms). This task was included to test whether congenital one-handers are generally slower then controls in verbal responses to related visual stimuli regardless of the task, or whether the slowing is specific to the hand laterality judgment task. A subset of 19 two-handed controls, 12 amputees and 12 congenitals participated took part in the category naming task. In an ANCOVA with Age as a covariate no group differences were found ($F_{(2,40)}$=0.06, p=0.94). A Bayesian ANCOVA performed using JASP v0.9.0.1 (Jasp Team, 2020) revealed a BF < 0.33, supporting the null hypothesis of no performance differences between groups in the control task (BF_{10}= 0.18, BF_{01}=5.43; See Figure S2).

Correlation with phantom hand motor control in amputees

In the main text, we report a significant correlation between phantom hand motor control (phantom finger tapping response time) and overall mean RT in the hand laterality judgement task. To rule out the possibility that this correlation is driven by general inter-individual differences in speed, we also measured participants' intact hand motor control (intact hand finger tapping response time) and created a measure of phantom motor control that accounts for intact motor control by using the phantom motor control residuals from the correlation between the two (intact and phantom hand motor control). The residuals, reflecting the unique contribution of phantom hand response times after accounting for inter-individual differences in speed, were then correlated with overall mean RT in the hand laterality judgement task using a Spearman correlation resulting in a significant relationship between phantom hand motor control and visual hand laterality judgements [r_s(13)=0.525, p=0.04]. Furthermore, to show that using the overall mean RT for all hand images in the hand laterality task is not driven by RTs for intact or missing hand posture image we've correlated each of them separately with phantom hand motor control, resulting in a correlation of $r_s(13) = .665$, $p = .007$ for intact hand images and $r_s(13) = .652$, $p = .008$ for missing hand images (see Figure S3).

References

Jasp Team. (2018). JASP (0.12.2).

van den Heiligenberg, F. M. Z., Yeung, N., Brugger, P., Culham, J. C., & Makin, T. R. (2017). Adaptable Categorization of Hands and Tools in Prosthesis Users. Psychological Science, 28(3), 395–398. https://doi.org/10.1177/0956797616685869

‘Easy’ Posture Images

‘Hard’ Posture Images

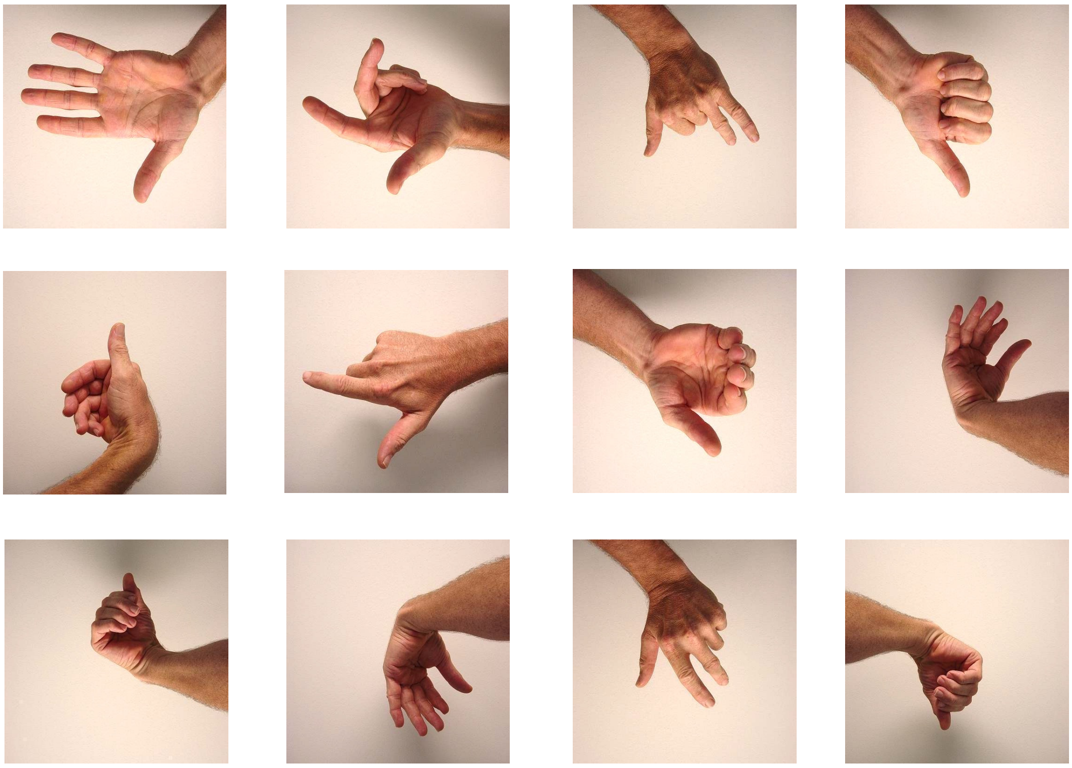


Figure S1. *Difficulty classifications for laterality hand posture images.* Hand postures were divided to easy and hard based on hand laterality judgement RTs from a separate control group.

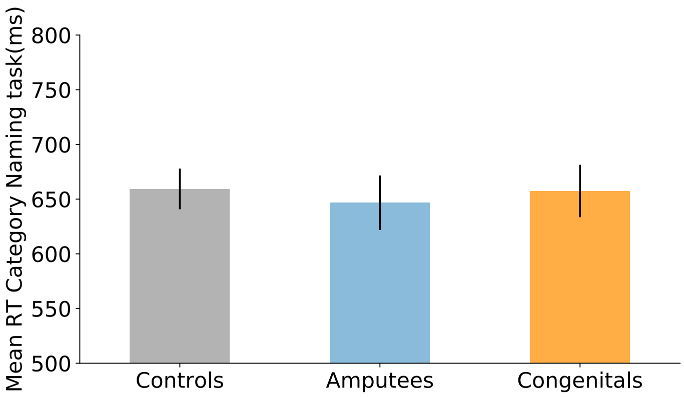


Figure S2. *Control visual category naming task.* RT group performance in the category naming task. Displayed are means ± standard error. No group differences found, as validated using a Bayesian analysis, pointing towards a lack of general cognitive deficit in congenitals relating to the current task setup.

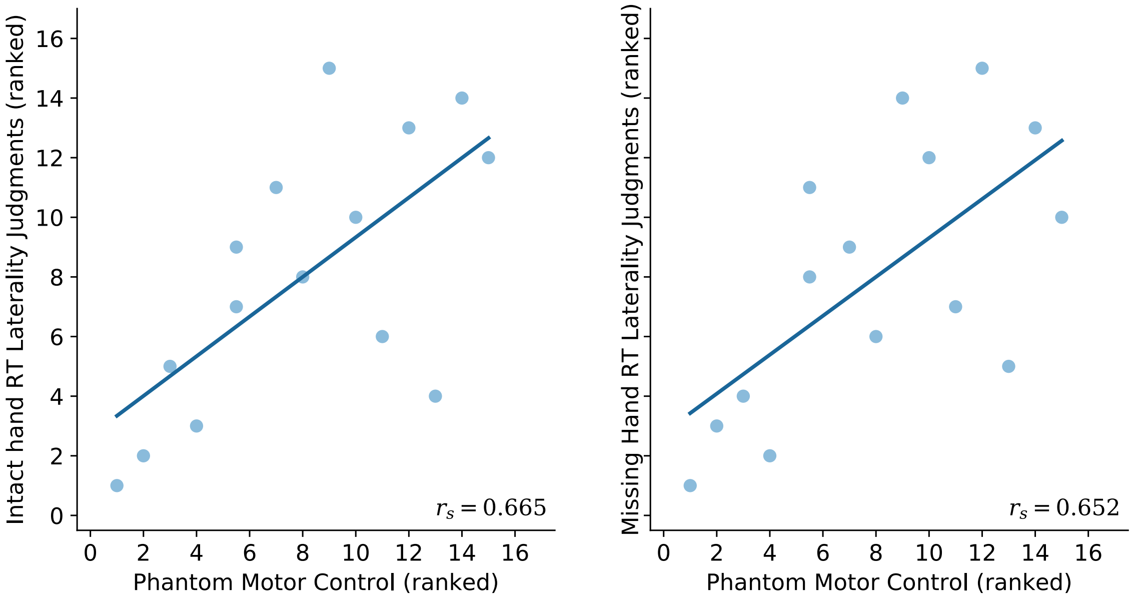


Figure S3. *Amputees phantom hand motor control correlated with hand laterality judgement performance for each hand side.* (A) mean RT (ranked) for images of the intact hand side in the hand laterality correlated to phantom finger-tapping RT (ranked), $r_s(13) = .665$, p = .007, (B) Missing hand RT laterality judgements (ranked) correlated to phantom finger-tapping RT (ranked), $r_s(13) = .652$, p = .008.

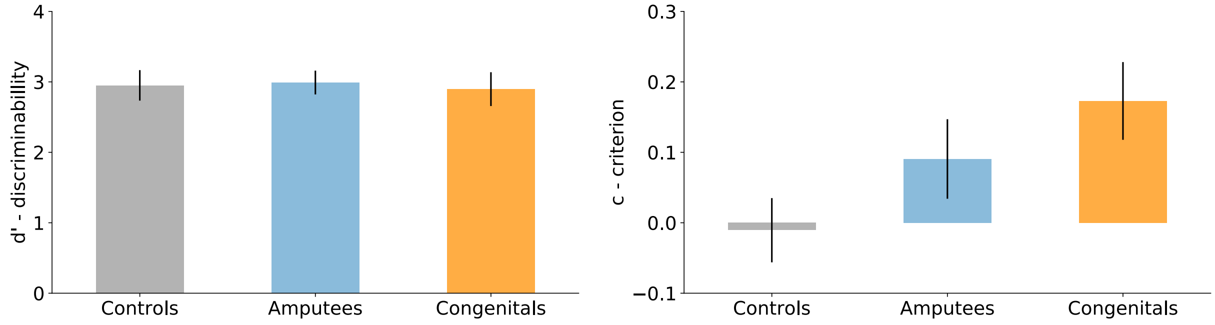


Figure S4. *Signal Detection Theory d-prime and c-criterion.* (A) d' group results, all groups show similar discriminability between intact and missing hand posture images (F(2,54)=0.04, p=.96). (B) Criterion (c) group results, congenitals show a bias to assume images are of their missing hand side (F(2,54)=3.31, p=0.04).

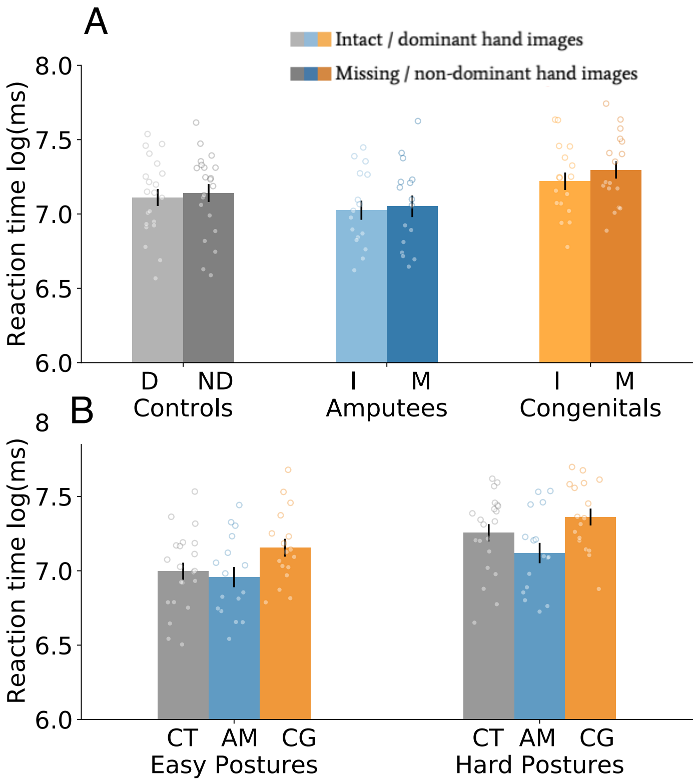


Figure S5. *Log-transformed RT plots.* (A) Group and individual performance (log-transformed RT values) in the hand laterality judgement task is shown for controls (grey), amputees (blue) and congenital one-handers (orange) for the intact and missing hands (light vs dark shades, respectively). Dots correspond to individual performance. (B) Group performance (log-transformed RT values) in the hand laterality judgement task in the hand laterality judgement task is shown for easy and hard postures in controls (grey), amputees (blue) and congenital one-handers (orange). Displayed are means ± standard error. CT=controls; AM=amputees and CG=congenital one-handers.

Effect	*df*	*F*	*p*
difficulty	50,1	18.296	<.001
difficulty * age	50,1	.024	.877
difficulty * group	50,2	4.696	.014
hand	50,1	1.850	.180
hand * age	50,1	.362	.550
hand * group	50,2	.970	.386
difficulty * hand	50,1	.810	.373
difficulty * hand * age	50,1	.242	.625
difficulty * hand * group	50,2	1.632	.206
age	50,1	.500	.483
group	50,2	3.226	.048

Table S2. *Results of reaction time (RT) rmANCOVA*

Effect	*df*	*F*	*p*
difficulty	50,1	.203	.654
difficulty * age	50,1	2.416	.126
difficulty * group	50,2	.988	.380
hand	50,1	.703	.406
hand * age	50,1	.045	.833
hand * group	50,2	3.920	.026
difficulty * hand	50,1	1.976	.166
difficulty * hand * age	50,1	.376	.542
difficulty * hand * group	50,2	.863	.428
age	50,1	.000	.988
group	50,2	.292	.748

Table S3. *Results of accuracy rmANCOVA*

Effect	*df*	*F*	*p*
difficulty	50,1	.377	.542
difficulty * age	50,1	2.786	.101
difficulty * group	50,2	1.337	.272
hand	50,1	.627	.432
hand * age	50,1	.077	.782
hand * group	50,2	3.338	.044
difficulty * hand	50,1	1.573	.216
difficulty * hand * age	50,1	.310	.580
difficulty * hand * group	50,2	1.770	.181
age	50,1	.249	.620
group	50,2	1.341	.271

Table S4. *Results of RT/accuracy rmANCOVA*. Though note that Box's Test of Equality of Covariance Matrices was significant (Box's M= 45.09, F(20,8386.36)=1.99, p= 0.005).

	Reaction time (seconds, *mean ± standard error*)	Accuracy (%, *mean ± standard error)*
Controls	1.278 seconds ± .317	90.5% ± 6.73
Amputees	1.176 seconds ± .319	91.7% ± 5.69
Congenitals	1.455 seconds ± .352	89.8% ± 8.04

Table S5. *Average group reaction time & accuracy values for all hand images.*

5.1.2 Supplementary Materials Chapter 2

Supplementary Text S1 - Supplementary results: ‘Hand’ and ‘Tool’ ROI analysis

To demonstrate that our results are not specific to the ROI definition used here for EBA, we’ve conducted the same analysis in ‘hand’ and ‘tool’ ROIs generated from the meta-analysis tool Neurosynth (Yarkoni et al., 2011) (https://neurosynth.org/analyses/terms/hand/, https://neurosynth.org/analyses/terms/tools/). Using the association maps for the words: ‘hand’ and ‘tools’, ROIs were defined by using all significant voxels within the OTC (see Methods for definition of OTC). It is important to note that there is some partial overlap between the ‘hand’ and ‘tools’ ROIs, particularly in the left hemisphere (see Figure S4). This is a known limitation of the spatial distribution of hand- and tool-selectivity in OTC, which is the primary reason we opted for an a priori independent ROI definition of EBA. Furthermore, as these ROIs were transformed from standard space and were not localised for each individual subject, the probabilistic ROI approach suffers from potential for reduced statistical power.

Both the ‘hand’ and ‘tool’ ROIs showed no significant visual hand-similarity (embodiment) group differences or correlation with prosthesis usage (p>0.2 for all). The ‘hand’ ROI showed a significant prosthesis-similarity (categorisation) group difference ($t_{(54)}$=-2.84, p=0.01), with prosthesis users showing a stronger categorisation effect, and a trend toward significance for the correlation with prosthesis usage ($r_{(30)}$=0.32, p=0.08). The ‘tools’ ROI did not show a significant categorisation prosthesis-similarity group effect ($t_{(54)}$=-0.56, p=0.58), but showed a significant correlation with usage ($r_{(30)}$=0.40, p=0.03).

Furthermore, when performing the ‘own prosthesis’ analysis, the Neurosynth ‘hand’ ROI showed a significant shift of the own prosthesis away from hands ($t_{(25)}$=6.70, p<0.001) but not away from tools ($t_{(25)}$=1.78, p=0.087). Neurosynth’s ‘tool’ ROI showed a significant shift of the own prosthesis away from both hands ($t_{(25)}$=4.19, p<0.001) and tools ($t_{(25)}$=4.3, p<0.001). This additional analysis confirms that our key findings in OTC are relatively robust.

Subject	Gender	Age	Non-Dominant Hand Side
PC01	F	70	Left
PC02	F	49	Left
PC03	M	27	Left
PC04	F	36	Left
PC05	F	24	Left
PC06	M	25	Right
PC07	F	52	Left
PC08	F	43	Left
PC09	M	27	Left
PC10	F	38	Left
PC11	M	52	Right
PC12	M	47	Left
PC13	M	41	Right
PC14	M	49	Left
PC15	M	28	Right
PC16	F	32	Left
PC17	F	42	Right
PC18	M	31	Left
PC19	M	44	Right
PC20	F	40	Left
PC21	M	52	Right
PC22	F	62	Left
PC23	F	25	Left
PC24	M	64	Right

Supplementary Table S1. *Control participants demographics.* This table was taken from the supplementary material of van den Heiligenberg et al., 2018 using the same controls cohort.

	Bilateral ROI	Left ROI	Right ROI
Hands	t(54) =-.91, p=.365	t(54) =-.92, p=.36	t(54) =-.81, p=.42
Tools	t(54) =.03, p=.975	t(54) =.32, p=.75	t(54) =.-14, p=.89
Active Prosthesis	t(54) =-1.2, p=.24	t(54) =-.97, p=.34	t(54) =-1.24, p=.22
Cosmetic Prosthesis	t(54) =-.29, p=.77	t(54) =-.38, p=.70	t(54) =-.13, p=.90

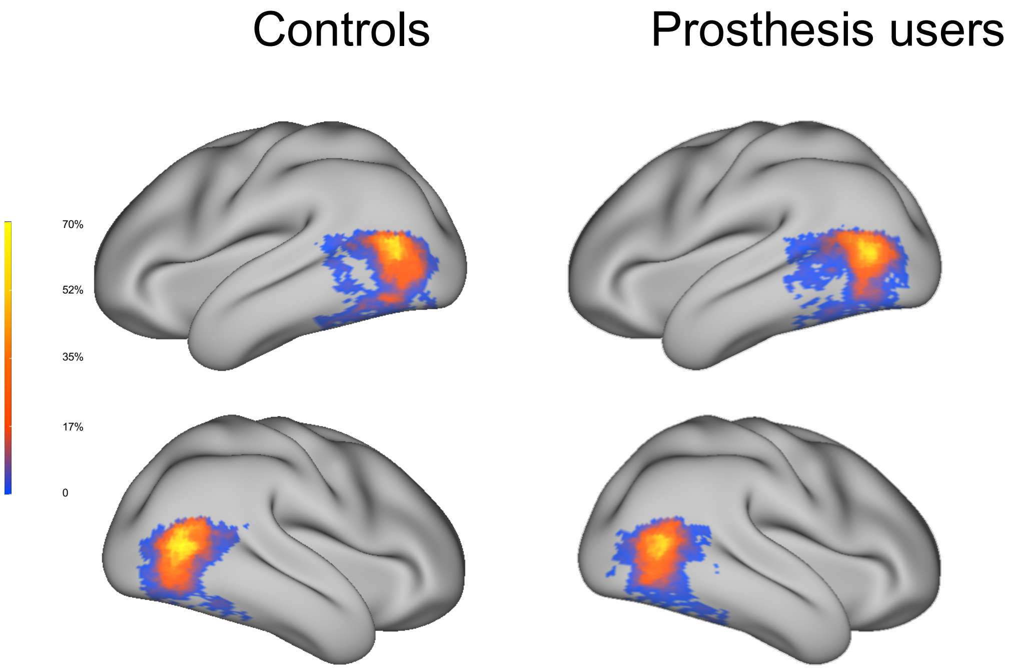
Supplementary Table S2. *Group Comparison of average activity levels between controls and prosthesis-users within the visual body-selective region of interest.* Results are shown for both the bilateral ROI (500 voxels) and for each hemisphere separately (250 voxels each)

	Bilateral ROI	Bilateral ROI Raw	Left ROI	Right ROI
Hand-Similarity index				
Group comparison	t(54)=0.47, p=0.64	t(54)=0.46, p=0.65	t(54)=-0.46, p=0.65	t(54)=0.54, p=0.59
Correlation with usage Pearson's R	r(30)=-0.03, p=0.85	r(30)=-0.02, p=0.91	r(30)=-0.05, p=0.80	r(30)=-0.02, p=0.91
Prosthesis-Cluster index				
Group comparison	t(54)=-2.55, p=0.01	t(54)=-2.55, p=0.01	t(54)=-2.66, p=0.01	t(54)=-2.25, p=0.03
Correlation with usage Pearson's R	r(30)=0.43, p=0.01	r(30)=0.42, p=0.02	r(30)=0.30, p=0.10	r(30)=0.43, p=0.02

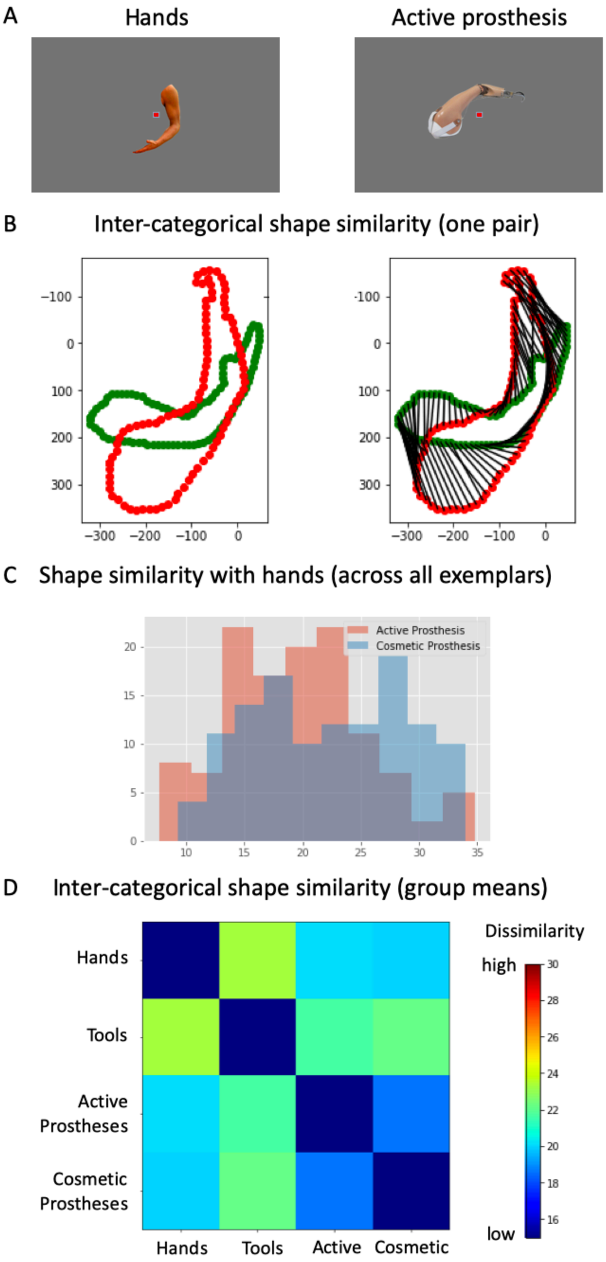
Supplementary Table S3. *A summary table for analyses of hand-similarity index and prosthesis-cluster index*. Group comparisons (controls vs. prosthesis users) and correlation with prosthesis usage. Including the results reported in the paper (bilateral ROI), results within the same ROI with the raw indices without controlling for the hand-tool distance (bilateral ROI raw), and for the results of the indices for each hemisphere separately.

Pairwise distance	1st component – 61.88% of variance	2nd component – 18.43% of the variance
Hands <-> Active Prostheses	.873	.025
Hands <-> Cosmetic Prostheses	.823	-.087
Tools <-> Active Prostheses	.616	**.725**
Tools <-> Cosmetic Prostheses	.907	.025
Cosmetic Prostheses <-> Active Prostheses	.674	**-.622**

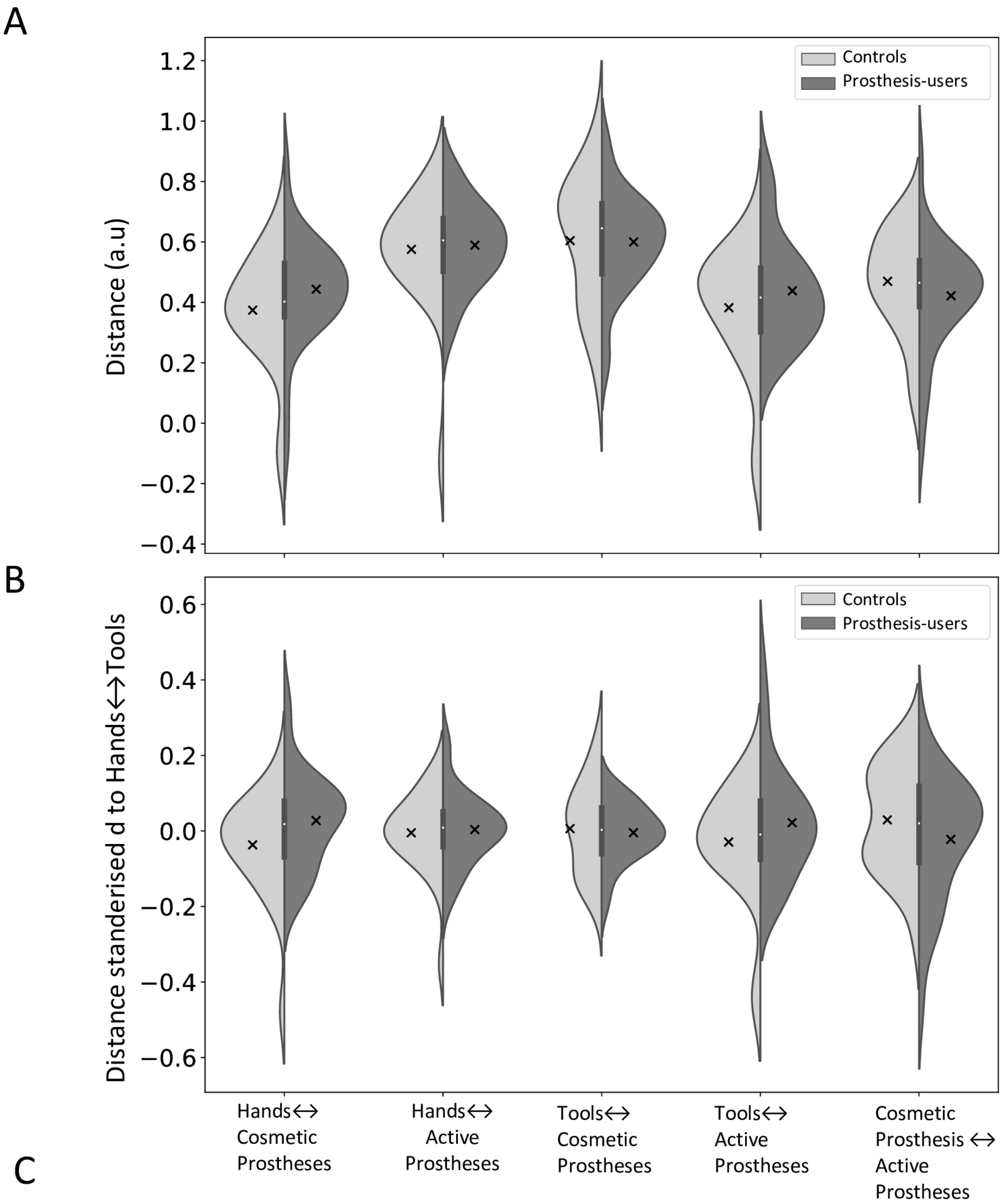
Supplementary Table S4. *Principle component analysis (PCA) of pairwise distances.* To explore which of the pairwise distances contributed to the underlying observed effect of prosthesis categorisation we ran a data-driven analysis (PCA) on the five distances of the one-handed group. Values in the table are the weights given to each distance within a component. The 1st component shows a 'main effect' of inter-individual differences across participants, in which some individuals have overall larger distances than others across all condition pairs. In our calculated indices we control for this effect by normalising individual's selectivity indices by their Hands<-> Tools distance (See Methods). The 2nd component explains almost half of the remaining variance (after accounting for the inter-individual differences in component 1). In the 2nd component, individuals showing greater distances between the active prostheses and the tool condition, also show greater similarity between the active prosthesis and the cosmetic prosthesis conditions. In other words, when the active prosthesis condition moves away from the tool category, it also tends to get closer to the cosmetic prostheses (as can be seen by the high weights and opposite signs of these two distances in the second component). This data-driven analysis provides further support for the hypothesised categorical shift of prosthesis representation.



Supplementary Figure S1. *Group probability maps for visual body-selective regions of interest (ROIs) in control participants and prosthesis users.* All individual visual ROIs were superimposed per group, yielding corresponding probability maps. Warmer colours represent voxels that were included in greater numbers of individual ROIs.



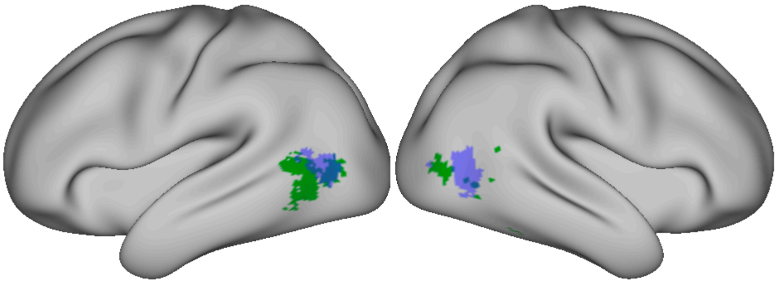
Supplementary Figure S2. *Intercategorical shape dissimilarities.* (A) Two exemplars from the 'hand' and 'active prosthesis' categories. (B) All exemplars shown to each individual participant were submitted to a visual shape similarity analysis (Belongie and colleagues, 2002), in which intercategorical pairwise shape similarity was assessed. (C) A histogram showing intercategorical similarity from one participant's shown cosmetic (blue) and active (red) prosthesis exemplars, with respect to hand exemplars (all exemplars are available on https://osf.io/kd2yh/). As demonstrated in this example, these dissimilarity ranges were largely overlapping. (D) This intercategory dissimilarity analysis was repeated for each of the participants (based on the specific prostheses exemplars shown to them), and mean histogram values were averaged. As indicated in the resulting matrix, cosmetic and active prostheses did not show strong differences in similarities, on average. This is likely due to the wide range of exemplars/shapes used in the study data set.



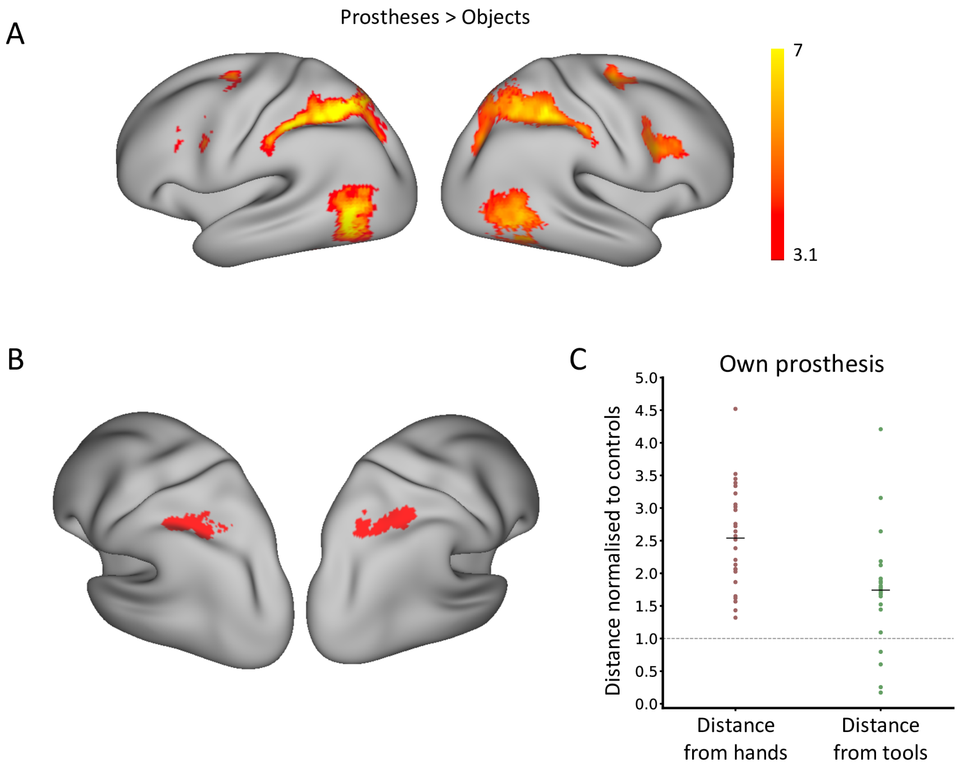
C

	Hands<-> Cosmetic Prostheses	Hands<-> Active Prostheses	Tools<-> Cosmetic Prostheses	Tools<-> Active Prostheses	Cosmetic Prosthesis <-> Active Prostheses
Hand similarity index:	↓	↓	↑	↑	-
Prosthesis similarity index:	↑	↓	↓	↑	↓

Supplementary Figure S3. Pairwise distances in EBA. (A) Pairwise distances between patterns of activations of hands, cosmetic prostheses, active prostheses, and tools. In the labels, '↔' indicates the distance between a pair of conditions. Within the plot, x indicates the group's mean. (B) same as panel A, only with each distance standardised by the individuals' distances between hands and tools. (C) A table illustrating the direction of the effect predicted by each index. Data used to create this figure can be found at https://osf.io/4mw2t/. EBA, extrastriate body-selective area



Supplementary Figure S4. *Neurosynth 'hand' and 'tool' ROIs.* Using the association maps for the words: 'hand' (blue) and 'tools' (green), ROIs were defined by using all significant voxels within the OTC. These ROIs are projected on inflated brain for visualisation.



Supplementary Figure S5. *Intraparietal Sulcus (IPS) analysis.* (A) Univariate activations in prosthesis users. Results of the group level univariate contrast of (Active Prosthesis + Cosmetic Prosthesis) > Objects show that at the group level the IPS is also activated. (B) The IPS region of interest was taken from the Juelich Histological Atlas (30% probability of hIP1, hIP2, and hIP3). (C) Hand (left) and tool (right) distances from users' 'own' prosthesis in IPS. Individual distances were normalised by the controls' group mean distance, depending on the visual features of the 'own' prosthesis (hand-likeness). A value of one indicates similar hand/tool distance to controls. Users showed significantly greater distances between their own prosthesis and hands (t(25)=10.11, p<0.001contrary to the embodiment hypothesis. A significant increase in the distance of the 'own' prosthesis from tools was also observed (t(25)=4.62, p<0.001).

5.1.3 Supplementary Materials Chapter 3

Speed-accuracy trade-off in prosthetic arm reaches

To test whether the three groups (controls, amputees and congenitals) use the same speed accuracy trade-off strategy. More specifically, whether prosthetic arm reaches follow the same control principles as biological arm reaches that have been shown to follow Fitts' law (Fitts 1954), a specific relationship between the movement time and the movement distance:

$$MT = a + b \cdot log_2(2D/S)$$

[MT: movement time, D: distance to target, S: target size – constant]

For each subject, we used a linear regression to obtain the parameters *a* and *b*. To test whether reaches of each group follow Fitts' Law equally, the r-squared value of the regression was compared across all groups as well as the regression parameters (using an ANCOVA, controlling for the parallel measure of the intact hand). To reduce the influence of noisy individual reaches, the reaches have been divided and averaged into 6 bins, based on their distance from the starting position. We found no group differences in either goodness of fit ($\boldsymbol{r^2}$: p=0.84, BF_{Incl}=0.167) or fitted parameters (***a****:* p=0.31, BF_{Incl}=0.347, **b***:* $p=0.61$*,* $BF_{Incl}=0.22$) between groups, indicating prosthetic arms reaches follow Fitts' laws and do not differ in their speed-accuracy trade-off strategy (see Figure S1, Table S4 for full statistical reports and https://osf.io/quyke/ for plots of individual participants).

Movement maximum velocity

For each participant, the maximum velocity of every trial was extracted and averaged across all trials. When comparing the mean velocity between groups (while controlling for the velocity of the intact hand), we found a significant relationship with intact hand velocity ($F_{(1,47)}$= 237.615, p<0.001, η_p^2=0.835) and a significant group effect ($F_{(2,47)}$=3.49, p=0.04, η_p^2=0.13). Post-hoc comparisons showed prosthetic arm reaches of amputees were slightly, but not significantly, faster than congenital one-handers (t=-2.31, p_{tukey}=0.06, *Cohen's-d*=-0.31).

Amputees were also slightly, but not significantly, faster than controls' non-dominant hand reaches (t=-2.37, p_{tukey}=0.06, *Cohen's-d*=-0.36). Congenital one-handers prosthetic arm velocities did not differ from those of controls (t=0.19, p_{tukey}=0.98, *Cohen's-d*=0.03). Importantly, these differences in velocities were not related to our main effect of group differences in reaching accuracy. When adding the maximum reaching velocities as a covariate to the main analysis described in section 3.1, all reported results remained significant and the effect of maximum velocity on absolute reaching error was not significant (F(1,46)= 0.27, p=0.61, BF_{Incl}=0.247).

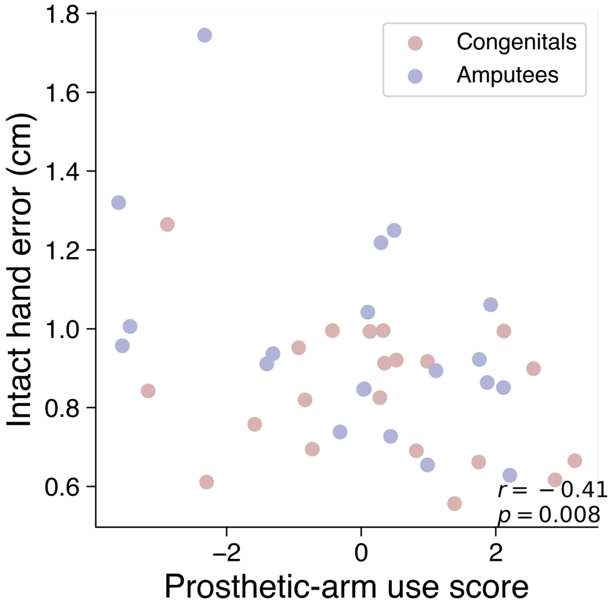


Figure S1. *Intact hand errors and daily prosthetic arm use.* We found a significant correlation ($r_{(39)}$=-0.41, p=0.008) between prosthetic arm daily use and intact-hand reaching errors. In this analysis, both prosthetic arm users' groups (congenitals and amputees) were analysed together as we found no differences in intact-hand errors between the groups. Daily prosthetic arm use was quantified using questionnaires relating to both wear-time and functionality of use.

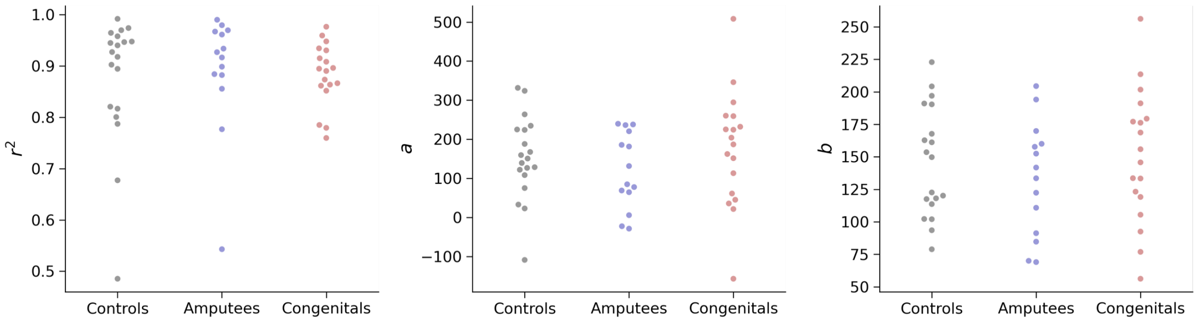


Figure S2. *Group values for Fitts law model fitting (r^2,a,b).* A linear regression was fit for each participant's reaches to obtain the Fitts law model's parameters a and b. Parameters, as well as goodness-of-fit (r^2), were compared across groups. We found no group differences in either goodness of fit (**r^2**: p=0.84, BF_{Incl}=0.167) or fitted parameters (***a***: p=0.31, BF_{Incl}=0.347, ***b***: *p=0.61,* BF_{Incl}=*0.22*) between groups, indicating prosthetic arms reaches follow Fitts' laws and do not differ in their speed-accuracy trade-off strategy

ANCOVA – Dependent variable: Prosthetic arm absolute errors

Factors	SS	df	MS	F	p
Group – Fixed factor	0.719	2	0.360	12.117	< .001
Prosthetic arm side – Fixed factor	0.033	1	0.033	1.119	0.296
Intact-arm absolute errors - Covariate	0.835	1	0.835	28.127	< .001
Group ✻ Prosthetic arm side interaction	0.013	2	0.006	0.216	0.807
Residuals	1.306	44	0.030		

Table S1. *Main analysis while controlling for prosthetic arm/nondominant-arm side.* Results of a follow-up ANCOVA analysis showing no effects of prosthetic arm side (L vs R) on prosthetic arm reaching errors. Our main finding of a significant group effect was also unaffected by accounting for the side of the arm making the reaches.

ANCOVA – Dependent variable: Prosthetic arm absolute errors

Factors	SS	df	MS	F	p
Group – Fixed factor	0.137	1	0.137	5.065	0.032
Residual-limb length- Covariate	0.042	1	0.042	1.565	0.221
Intact-arm absolute errors - Covariate	0.318	1	0.318	11.768	0.002
Residuals	0.758	28	0.027		

Table S2. *Main analysis while controlling for residual-limb length.* Results of a follow-up ANCOVA analysis showing no effects of residual-limb length on prosthetic arm reaching errors. Our main finding of a significant group effect was also unaffected by accounting for residual-limb length. Note that this analysis only includes prosthetic arm users (amputees and congenitals) as controls have a complete arm and therefore no residual-limb length.

ANCOVA – Dependent variable: Prosthetic arm error noise

Factors	SS	df	MS	F	p
Group – Fixed factor	1.434	2	0.717	12.405	< .001
Prosthetic arm bias - Covariate	0.404	1	0.404	6.991	0.011
Intact-arm noise - Covariate	0.460	1	0.460	7.962	0.007
Residuals	2.659	46	0.058		

Table S3. *Comparing prosthetic arm error noise while controlling for prosthetic arm bias.* Results of a follow-up ANCOVA analysis showing that while there is a significant relationship between bias and noise, the group differences in error noise are independent of bias.

ANCOVA – ***r*² Prosthetic arm**

Factors	**SS**	**df**	**MS**	**F**	**p**
group	0.003	2	0.002	0.175	**0.84**
*r*² Intact	0.072	1	0.072	7.587	0.008
Residuals	0.447	47	0.01		

Bayesian ANCOVA

Analysis of Effects **– *r*² Prosthetic- arm**

Effects	**P(incl)**	**P(incl|data)**	**BF** $_{\text{incl}}$
group	0.5	0.143	**0.167**
*r*² Intact	0.5	0.854	5.852

ANCOVA – ***a* Prosthetic- arm**

Factors	**SS**	**df**	**MS**	**F**	**p**
group	27481.713	2	13740.857	1.211	**0.307**
a Intact	158782.482	1	158782.482	13.998	< .001
Residuals	533131.773	47	11343.229		

Bayesian ANCOVA

Analysis of Effects **– *a* Prosthetic- arm**

Effects	**P(incl)**	**P(incl|data)**	**BF** $_{\text{incl}}$
group	0.5	0.258	**0.347**
a Intact	0.5	0.982	53.771

ANCOVA – ***b* Prosthetic- arm**

Factors	**SS**	**df**	**MS**	**F**	**p**
group	1378.606	2	689.303	0.498	**0.611**
b Intact	35615.379	1	35615.379	25.73	< .001
Residuals	65056.014	47	1384.171		

Bayesian ANCOVA

Analysis of Effects – ***b* Prosthetic- arm**

Effects	**P(incl)**	**P(incl|data)**	**BF** $_{\text{incl}}$
group	0.5	0.178	**0.217**
b Intact	0.5	1	3856.606

Table S4. *Frequentist and Bayesian analysis of model fitting reaches data to Fits' Law*. Full statistical report of group comparisons of model's parameters a and b as well as goodness-of-fit (r^2) of the linear regression model. No differences were found across groups.

5.2 Appendix A - Peri-hand space representation in the absence of a hand–Evidence from congenital one-handers (published PDF)

5.3 Appendix B - Expert tool users do not visually embody their hand-held tool (published PDF)

5.4 Appendix C - Talking with your (artificial) hands: communicative hand gestures as an implicit measure of embodiment (published PDF)