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THE MOTOR CORE OF BODY OWNERSHIP

Candidate:

FRANCESCO DELLA GATTA

PhD Advisor:

PAOLA ALICE BORRONI

PhD Coordinator:

MARCELLO MASSIMINI

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ABSTRACT

The present work deals with one of the most fascinating aspect of consciousness, the awareness of the bodily-self, and in particular with the notion of body ownership. The goal of this thesis is to combine the phenomenological conception of the bodily-self, mainly grounded on the concept of embodiment, with the scientific investigation of the physiological bases of the sense of body ownership. Chapter 1 introduces the theoretical subject and its experimental investigation in both pathological and healthy brain, arguing that the very core of the self, as claimed by neuro-phenomenology, is determined by the dynamic relationship between body representation and motor system, which enables human beings to properly act in the world and to build a coherent sense of self. In this view, body representation and the possibility to move are conceived as the two main factors allowing human beings to reach a conscious experience of the self. Can this theoretical insight meet scientific evidence? In other words, are we able to *measure* the contribution of the sensory-motor system in generating body ownership? This aspect of human experience was investigated using two experimental approaches. In Chapter 2, given that the fundamental characteristics of subjectivity can sometimes be illuminated through the study of their pathological distortions, we experimentally tested how body metric representation can be susceptible to plastic remapping after tool-use training, in healthy subjects (Experiment 1) and in a particular sample of patients in which an ischemic episode in the right hemisphere caused a disruption of body ownership, along with primary sensory-motor dysfunction (Experiment 2). These patients show a sort of complementary disease to the well-described symptoms of patients in classical somatoparaphrenia (delusion of dis-ownership), by showing a *pathological embodiment* of someone else's limb (delusion of ownership). As is often the case with neuropsychological syndromes, a large amount of theoretical questions arises from the observation of this condition. First of all, which is the phenomenal experience involved? Is that condition just a confabulatory manifestation? Does

this subjective and sometimes illusory sense of body ownership influence objective measures of the sensory-motor system? Which is the relationship between sensory-motor impairment and body ownership disruption? Chapter 2 addresses these questions by demonstrating that the intentional motor processing which underlines the action execution with an alien limb experienced as own, induces body representation remapping, even in absence of actual proprioceptive feedback. Chapter 3 investigates how a multisensory illusion that alters the sense of body ownership, the *rubber hand illusion* (RHI), affects the activity of the motor system in a sample of healthy subjects. During this experimental manipulation, subjects report a feeling of ownership over an artificial, rubber hand and a concurrent feeling of dis-ownership over their real hand. What is the mechanism underlying the self-attribution of the rubber hand to one's own body? And again, which relationship is there between the functionality of the sensory-motor system and the feeling of body ownership? Are the qualia of ownership/dis-ownership reflected at the level of the motor system? We found that the sensation for the *hand disappearing* is reflected in a lower excitability of the motor pathways that govern the movement of the same hand, providing the first neurophysiological evidence that our conscious experience to *have or not* a body has a fundamental counterpart in the activity of the sensory-motor system. In conclusion, even if usually taken for granted, our conscious belief to own a body has a very multi-level nature. Both in presence of brain injuries and experimental manipulation, the sense of body ownership can be altered; only in these cases we are able to realize the complexity of its structure and how the brain plays an essential part in its generation. The results reported here are discussed in the context of phenomenological and cognitive literatures in an effort to understand the role of both body awareness and of sensory-motor activity as the building stones of the human conscious experience of being in the world.

Chapter 1

1. GENERAL INTRODUCTION

1.1 A body centered conception of the self, a multidisciplinary approach.

Philosophers, psychologists and cognitive neuroscientists have widely discussed the notion of the body as the basis, or the starting point for our conscious experience. In the ongoing debate on the definition of Self-consciousness philosophers and cognitive neuroscientist are emphasizing the essential role of the body, conceived as the constitutive source of pre-reflective self-consciousness. This process of integration between phenomenological analysis and naturalistic models (Gallagher, 2006; Gallagher and Zahavi, 2008; Parnas, Zahavi, 2000; Petitot et al., 1999; Varela, 1987; 2001; Zahavi, 2004) can be indicated as a *recorporealization* of the Self (Csordas, 1990; Thompson and Varela, 2001; Heiner, 2008). If we put the body at the center of the scene, the conceptualization of the mind given from enactivism* captures very well the significance of this process: "*cognition depends upon the kinds of experience that come from having a body with various sensorimotor capacities and that these individual sensorimotor capacities are themselves embedded in a more encompassing biological, psychological, and cultural context*" (Varela et al., 1991, pp 172-173). In this view, as pointed out in Fuchs, Sattel and Henningsen (2010), "*Embodiment refers not only to the embedding of cognitive processes in brain circuitry, but also to the origins of these processes in an organism's sensory-motor experience in relation to its environment*". It follows that even if the Self is a complex, multileveled and multidimensional notion (Parnas, 2000; 2003) "*there is a basic, immediate or primitive something that we are willing to call self*" (Gallagher, 2000, p. 15), or, in other words, "*the feeling of the same old body always there*" (James, 1890). As underlined by Merleau-

Ponty (1945), "*my body appears to me as an attitude directed towards a certain existing or possible task*" and it makes possible our understanding of the environment as a space of likely engagements and actions. In this perspective the bodily-self is conceived not only as an integrated system, characterized by matching of sensory-motor information (Legrand 2006, p. 111), but also as power for action, a "*sense of body that is enactive" in nature and that enables to capture the most primitive sense of self*" (Gallese and Sinigaglia, 2010).

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*According to *enactivism*, the mind emerges from a dynamic interaction between an acting organism and its environment. In this approach, cognition can only be understood if conceived as embedded in a total "biological/psychological, and cultural context" (Varela et al., 1991: 172-173); claiming that cognition *"is based on situated, embodied agents*" (Varela, 2001: 215) bring to an explicitly rejection of *representationalism* (what we consciously perceive is the result of a copy of the *external* world in an *internal* representation). The mind "*cannot be separated from the entire organism*" (Varela, 1999: 73), because "*knower and known, mind and world, stand in relation to each other through mutual specification or dependent co-origination*" (Varela et al., 1991: 150). Because the mind is embodied and arises out of "*an active handling and coping with the world*", "*[t]he mind is not in the head*" (Varela, 1999: 72) and then "*whatever you call an object ... is entirely dependent on this constant sensory motor handling*". Therefore, an object is never independently "out there", but "*arises because of your activity, so, in fact, you and the object are co-emerging, co-arising*" (Varela, 1999: 71-72). In conclusion, the "*organism and environment enfold into each other and unfold from one another in the fundamental circularity that is life itself*" (Varela et al., 1991: 217).

Accordingly, also recent neuroscientific theories have suggested that perception and cognition are fundamentally *shaped* by the body (Barsalou, 2008; Gallagher, 2005; Gallese & Lakoff, 2005; Proffitt, 2006). A good starting point to face this concept of minimal or "core self" (Damasio, 1999; Rochat, 2004; Zahavi, 2005) is by focusing on the notion of *body ownership,* conceived as the feeling that our body parts belong to us. Both philosophy (Husserl, 1936, 1931; Merleau-Ponty, 1962) and natural sciences (Head & Holmes, 1911; Gallese & Sinigaglia, 2010; 2011) explain what body ownership is by referring to two fundamental concepts: *body schema* and *body image*. The first one is a

representational model of the body, built upon bottom-up processes, which provides a standard reference for both posture and movement (Head & Holmes, 1911; Gallagher, 1998). This model results from previous sensory-motor experiences, mainly involving the sense of proprioception, but also tactile and vestibular input (Berlucchi & Aglioti, 1997; 2010; Maravita et al., 2003), as well as motor control. It has also been argued that the body schema is nothing more than the implicit knowledge we have about our bodies, primarily composed by sensory-motor skills and habits:

"We have a sense of the body in what it accomplishes. I have a tacit sense of the space that I am in (whether it is crowded, whether it is wide open, or whether it is closing in). Likewise, I have a proprioceptive sense of whether I am sitting or standing, stretching or contracting my muscles. Of course, these postural and positional senses of where and how the body is tending to remain in the background of my awareness; they are tacit, recessive. They are what phenomenologists call a "pre-reflective sense of myself as embodied" (Gallagher & Zahavi, 2008, p.139).

A first description of this sub-component of bodily experience has been provided by the founder of phenomenology, Edmund Husserl. He named the body schema as *leib*, the *body-subject*, *lived* from inside, which recalls the subjective experience of the body from the first-person perspective. Accordingly, neuroscientists describe the body schema as intrinsically linked to voluntary action: it is updated during action, and also supports well-organized, smooth action by providing a proprioceptive representation of the initial conditions for the movement (Ghezet al, 1995; Sainburg et al, 1993; Tsakiris 2010). On the other hand, body image is defined as an explicit mental representation of our body, built upon top-down processes, which consist in a conscious belief about our body in terms of dimension, shape and specific features (Longo, 2009), and implies also the

emotional feeling towards it (Slade, 1988; Cash and Brown, 1987; Gardner and Moncrieff, 1988; Powers et al, 1987). Husserl captures the notion of body image as *korper*, the *body-object observed* from outside, which is the experience of our body from a third person perspective (Drummond, 2007). The continuous interface between these two aspects is responsible for the appearance of body ownership (Merleau-Ponty, 1962). Correspondingly, cognitive neuroscientists report that the interactions between bottom-up and top-down components are a necessary condition for the appearance of the body ownership (Tsakiris, 2010). These processes, which take place in multisensory associative brain areas (Blanke et al., 2015), define ourselves as *having* a certain body distinct from the other objects of the world. In this last essential interplay, a fundamental process that underlines our conscious experience to own a body is indicated as *embodiment,* which corresponds to a specific type of information processing of perceptual, motor and cognitive conditions for a body part to be experienced as one's own (de Vignemont, 2011). This term has been introduced to replace the classical theory proposed by Decartes, which postulated a separation between the mind (res cogitans) and the body (res extensa). By contrast, in a neuro-phenomenological perspective, every cognitive experience, from perceptual-motor behavior to human reasoning, arises through the concurrent participation of several functionally distinct and topographically distributed regions of the brain and their sensorimotor embodiment (Varela et al. 2001). According to Gallagher & Zahavi, "*it just is an empirical fact that we are indeed embodied, that our perceptions and actions depend on the fact that we have bodies, and that cognition is shaped by our bodily existence*" (2008, p 131). To summarize, body ownership is a complex conscious phenomenon, composed by distinct aspect of our body perception: an *unconscious* body schema, a *conscious* body image, and a dynamic relationship between the two captured by the process of embodiment. At this point, a fundamental issue urges to be addressed: where are the boundaries

between us and the world? Alva Noe claims that there is no reason to believe that our bodies end where we usually think: "*parts of me, such as tools, can be physically separated from my body; what makes it part of me is the way in which they are involved in my actions*" (2010). The possibility to execute an action, intrinsic feature of our body schema, can shape the way in which we represent ourselves with respect to the environment in which we act (Thompson & Rosch, 2001). When we use a pen, a tong or a rake, it is as though the tool has become part of ourselves; the process and experience of embodiment highlights the plasticity of the self, extremely dynamic, in constant development with the environment in which it is situated (Maturana & Varela, 1987).

In the last thirty years, the concept that our conscious belief to possess a body is not something rigid and fixed from our birth, but is rather constantly taking shape in the mutual interaction with the environment (which recalls what James (1890) tried to capture with the expression "*flow of experience"),* has started to gain recognition also in basic neuroscience. Intracranial electrophysiology studies have identified several fronto-parietal networks responsible for the integration of information from specific body regions and external space, and shown how such integration is functionally relevant to specific actions performed by specific body parts (Colby, 1998; Rizzolatti et al., 1997, 1998; Graziano & Gross, 1998; Jeannerod et al., 1995). Those neurons are named *bimodal* neurons because they respond both to somatosensory information from a specific body part and to visual information from the space adjacent to it (Graziano et al., 1994; Fogassi et al., 1996; Duhamel et al., 1996). Moreover, the visual receptive field of bimodal neurons remains *anchored* to the body segment when this moves in space; therefore, it has been proposed that this system may be crucial for coding action space in body-centered coordinates (Colby, 1998; Graziano & Gross, 1998; Ladavas, 2002). It is now well accepted that these areas of integration of multisensory signals (visual, somatosensory and, in the case of *trimodal* neurons, also auditory) constitute the

neural substrate coding for *peripersonal space* (PPS). For example, for the hand PPS is defined as the "hand reaching space", immediately surrounding the body, in which objects can be grasped and manipulated (Di Pellegrino & Ladavas, 2015). It has been shown that bimodal neurons anchored to the monkey's face expand their receptive fields when a stimulus approaching the animal's face increases its speed motion (Fogassi et al., 1996). Similarly, a very elegant experiment by Iriki, Tanaka and Iwamura (1996) has shown that visual receptive fields of bimodal (visuo-tactile) neurons of the macaque' posterior parietal cortex, active during hand movements, can be modified by actions which involve use of tools. After having trained monkeys to retrieve pieces of food with a small rake, the researchers noticed that during active tool use the receptive visual fields anchored to the monkey's hand become large enough to include the space around both hand and rake. In animals that handled the rake for the same amount of time but without the training for purposeful use the receptive fields maintained their usual extension (Figure 1.1 and 1.2).

Distal-type neurons
(a) (b) Before tool-use (c) After tool-use (d) Passive holding
sRF

Proximal-type neurons
(e) (f) Before tool-use (g) After tool-use
sRF

TRENDS in Cognitive Sciences
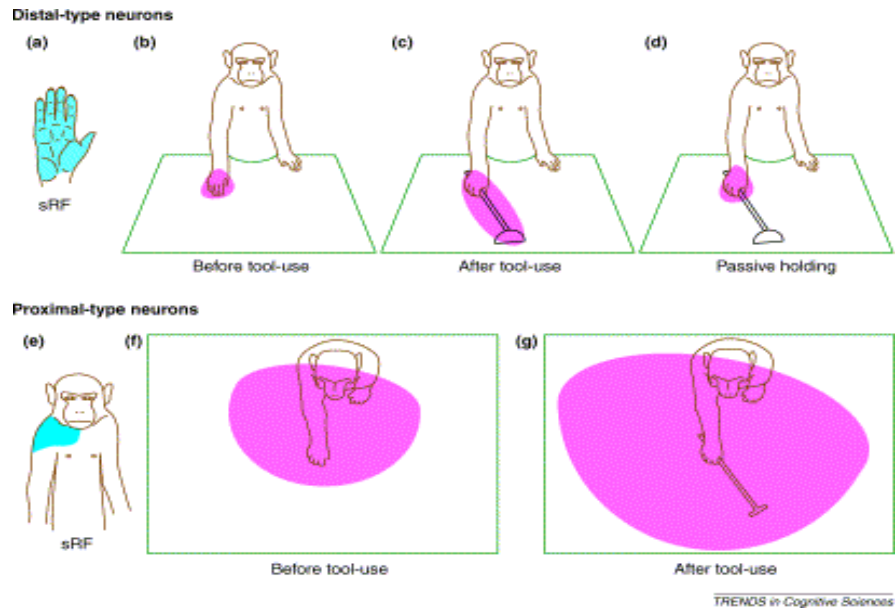
FIG 1.1. Changes in bimodal receptive field properties following tool-use. The somatosensory receptive fields (sRF) of cells in this region were identified by light touches, passive manipulation of joints or active hand-use. The visual RF (vRF) was defined as the area in which cellular responses were evoked by visual probes. (a) sRF (blue area) of the 'distal type' bimodal neurons and their vRF (pink areas) (b) before tool-use, (c) immediately after tool use, and (d) when just passively grabbing the rake. (e) sRF (blue area) of 'proximal type' bimodal neurons, and their vRF (pink areas) (f) before and (g) immediately after tool-use. (Image and caption adopted from *Maravita e Iriki, 2004*).
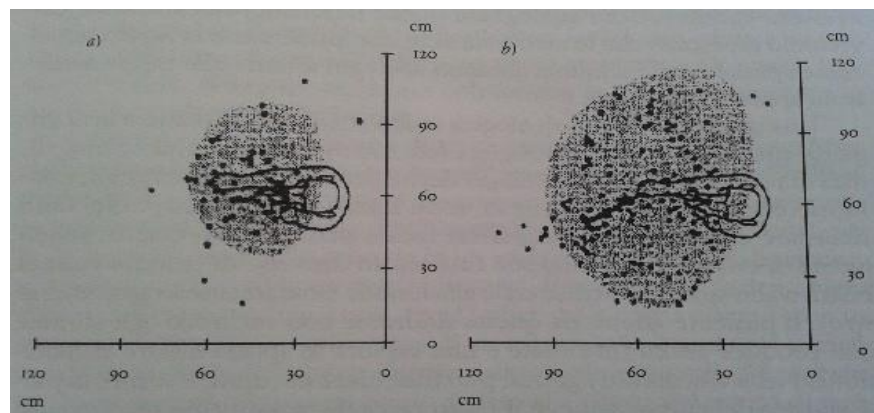
FIG 1.2. Expansion' of the hand-centered visual receptive fields of macaque monkey area 2 & 5 (anterior /medial bank IPS) neurons'. In a) monkey grasp food using the hand, in b) using a rake (receptive field become larger) (Image adopted from *Iriki, Tanaka, Iwamura, 1996*).

This physiological result is taken as evidence supporting the dynamic property of spatial representations: the instrument used to perform an action was included in the animal's body schema, which was expanded accordingly; as a consequence, the space that was previously coded as "far" by the bimodal neurons, after training is processed as "near" space, thanks to the dynamic extension of their receptive fields determined by the use of the tool.

A reshaping of similar spatial maps has also been observed in humans by studying a neuropsychological syndrome called *unilateral spatial neglect*. Neglect is a very complex and multi-faceted disease, mainly resulting from focal lesions of fronto-parietal circuits in the right hemisphere, often of ischemic origin, and entailing a deficit of awareness of space contralateral to the lesion (Marshall & Robertson, 2013). Berti & Frassinetti (2000) have analyzed the behavior of a patient who showed more severe neglect in PPS then in far space (out of hand reaching) and that, when asked to indicate the midpoint of lines designed on a sheet of paper, showed the usual rightward bias when performing with a laser pen the line bisection task, but not when pointing the laser pen in the far space. Interestingly, when the patient performed the task in the far space with a long wand allowing her to *physically* reach the line, the classical rightward bias re-emerged. The tool-use literally made the far space become near, possibly by extending the PPS to incorporate the wand in it (Berti & Frassinetti, 2010). The opposite remapping direction (the near space becoming far) has also been described. Neppi-Mòdona et al. (2007) observed that when using a laser pen (a tool that does not involve sensory continuity with the target) in line bisection tasks, patients remapped the near space as far; in this condition, the neglect bias in the near space became as severe as in the far space. This evidence suggests that processing the space as near implies a continuity between the instrument and the object, otherwise, the lack of visual, tactile and proprioceptive feedback from

the same instrument in the far space, point to a representation of the space as far (Neppi-Mòdona et al., 2007).

Evidences for a dynamic representation of *body-in-space* are also described in healthy subjects. Sposito and colleagues (2012), investigating to what extent the somatosensory representation of the body may be susceptible to remapping processes due to tool use, reported that participants, after a tool-use task, indicated the midpoint position of their limb (identified through tactile stimulation) more distal with respect to the pre-training measurement. This result has been widely replicated and is in line with the hypothesis of an extension of the body representation caused by the use of the tool (Cardinali et al, 2009; Iriki et al, 1996; Maravita et al, 2002; Costantini et al., 2011). A likely interpretation on the data is that the extension of the scope for action was critical in determining an extension of the internal representation of the length of the arm. Overall, these results indicate the existence of a deep relationship between body schema, action execution and space representation, brought about by multisensory and motor processing within the same associative brain areas, which provides the interface between perception and action (Brozzoli et al., 2012).

1.2 Body ownership alteration following brain injuries.

In the previous sections we have seen that a normal interaction with the world implies the implicit notion that the body executing actions in space is *mine*. Moreover, this conscious experience to own a body is constructed also on the contribution of a specific sensory-motor network responsible for coding space in a body-centered reference frame. But what happens when the sense of body ownership is dramatically altered as, for instance, after brain damage? In brain-damaged patients with motor and somatosensory impairments, body awareness can be pathologically altered. In some cases, patients may feel a sense of dis-ownership towards their contralesional limbs, because they

are *felt as separated* from their own body. Moreover, the feeling of strangeness may result in the delusional belief that the contralesional limbs do not belong to one's own body but to another person; this is the case of *somatopharafrenia* (Garcin et al, 1938; Gerstmann, 1942; Vallar and Ronchi, 2009; Romano et al., 2014). The lesional pattern recently associated with somatoparaphrenia reveals the function of a complex and distributed right fronto–temporo–parietal network extending to subcortical structures (Gandola et al., 2012), and to the insula (Karnath et al., 2010). In other cases, a more complex *denial* process of body parts may appear as a symptom resulting from injury of fronto-parietal cortex. This condition, called *misoplegia* from the greek "aversion to them" (Critcley, 1974; Moro et al., 2004), comprehends a dislike or hatred of one's own paralyzed limb, with verbal aggression towards it, and also including physical acts such as striking and beating the hemiplegic extremity (Loetscher et al., 2006). To enhance the complexity of this picture another syndrome, indicated as *xenomelia*, the "foreign limb syndrome" or "body integrity identity disorder" (BIID) has been described, characterized by the non-acceptance of one or more of one's own extremities and the resulting desire for elective limb amputation or paralysis (Brugger et al., 2013; Hilti et al., 2013). Interestingly, it has recently been shown that these patients have reduced cortical thickness and dimension in the superior parietal lobule and reduced cortical surface area in the inferior parietal lobule, somatosensory areas SI and SII, anterior insular cortex, and frontal operculum (Hilti et al., 2013). Crucially, all the described syndromes have in common the alteration of several fronto-parietal networks involved in multisensory integration processes, which make these areas the best candidate as the neural counterpart of a coherent sense of body ownership.

The majority of such body ownership disorders results in a disruption of the continuity of the self, which entails patients to refuse the ownership of a portion of their body which they don't physically feel as their own anymore. The possibility of the existence of an opposite behavior (patients who

mis-identify other people's limbs as their own) has rarely been considered. However, in recent studies (Garbarini et al., 2012; 2013a, 2014; Garbarini and Pia, 2013; Pia et al., 2013a), this behavior has been observed in a sample of patients who claimed that the examiner's left hand was their own whenever it was positioned, in egocentric coordinates, next to their left hand. Patients with this delusion of ownership, called *pathological embodiment*, don't deny their contralesional limbs (as in the somatoparaphrenic delusion of disownership) and treat the experimenter's left arm as if it is their own (see Chapter 2 for a more detailed description). Previous studies demonstrated that the pathological embodiment reflects a high-order cognitive mechanisms capable of altering the patients' sensory-motor functions. For example, using a modified version of the bimanual circle-line task, patients were asked to draw lines with their right hand (healthy) while watching an alien left hand draw circles in egocentric position, congruent with the patient's body image (condition in which the incorporation phenomenon occurs). They showed a significant interference effects of the alien arm movements on the actual movements of their own intact arm, resulting in a clear coupling effect as that observed in healthy control (Garbarini et al., 2013). Moreover, when painful stimuli were delivered to the alien *embodied* hand, patients referred to feel pain on it (Pia et al., 2013a) and showed coherent physiological skin conductance reactions, as if the own hand was stimulated (Garbarini et al., 2014). These results show how parts of the body belonging to other individuals may be, at least in pathological conditions, so deeply integrated in patients' sensory-motor system to generate intense sensory experiences such as those experienced on their real limbs.

In Chapter 2 we asked whether this altered sense of body ownership, i.e. pathological embodiment, can modulate both intentional motor processes and the spatial extension of the own body representation. In particular, we investigated the effects of the observation of an alien arm (which was pathologically embodied by patients) performing a tool-use training (grasp-to-place task) on the

representation-size of own forearm. The crucial aspect of this experiment is that we expected patients to truly believe to be actually performing the task with their own arm and, consequently, to show an overestimation of their forearm length in the post-training phase with respect to the pre-training phase. According to previous evidences (Sposito et al., 2012; Cardinali et al, 2009; Iriki et al, 1996; Maravita et al, 2002; Costantini et al., 2011), we expected to find an overestimation of the forearm length in a control group of healthy subjects (Experiment 1) only after active tool-use training, and the same effect in patients only when they pathologically embodied the alien arm performing the task (Experiment 2). Results in this direction would strongly support the view that the sense of body ownership extends to intentional motor processes but also modulates the sensory map of action-related body parts even in absence of active performed movement (in patients with pathological embodiment).

1.3 Body ownership alteration following experimental manipulation: the case of the rubber hand illusion.

The results presented so far show that bodily experiences must be understood in light of a multimodal representation of the body. It has been proposed that multisensory integration, together with internal models of the body, modulate the experience of the body as being one's own, as well as the demarcation or distinction between one's body and other objects (Tsakiris et al., 2010). Under normal circumstances, body schema and body image together form a consistent basis for self-consciousness. On the other hand, in unusual circumstances such as brain damage (see chapter 2) or multisensory illusions in healthy subjects (see chapter 3), the sense of body ownership can be

altered or manipulated (Gallagher and Cole, 1995; Paillard, 1999; Rossetti et al, 1995; Costantini and Haggard, 2007).

The *rubber hand illusion* (RHI) is an experimental paradigm that allows controlled manipulation of the experience of the feeling to own a body, and provides an incredible evidence for plasticity of embodiment. It has been shown that watching a rubber hand (RH) being stroked synchronously with one's own unseen hand is sufficient to produce a feeling of ownership over the fake hand (Botvinick and Cohen 1998). Briefly, during this experimental manipulation, participants see a rubber hand aligned in a similar orientation to their actual, unseen right hand (Figure 1.3). In the *synchronous* condition, the two hands (rubber and real hidden one) are touched at the same time with identical brushes at identical locations. For many participants, this visuo-tactile match generates the compelling feeling that the rubber hand *really* is their hand (i.e., the sense of ownership). In the *asynchronous* condition, in contrast, the two hands are touched at different times, eliminating the multisensory match between vision and touch and the participant's feeling of ownership over the rubber hand. The subjective feeling of ownership over the rubber hand is measured with a questionnaire which evaluate the subjects' vividness of illusion using items like: "It seemed as if I were feeling the touch in the location where I saw the rubber hand touched", "It seemed as though the touch I felt was caused by the touch over the rubber hand", "I felt as if the rubber hand were my hand". In the synchronous condition subjects tend to highly agree with those statements (but not in the asynchronous control condition). Moreover, when participants are asked to localize the perceived position of their unseen hand (for instance, by pointing with the opposite hand or by indicating a number on a ruler), they misjudged their real hand's location significantly more towards the RH; this behavioral component, named *proprioceptive drift*, is a multimodal measure which

combines the processing of visual, tactile, and proprioceptive information and suggest that, after the instauration of the illusion, the subject's hand-centered reference frame shifts towards the fake hand. In sum, the RHI has two behavioral components: reported feeling of ownership over the RH (questionnaire rating) and changing in the felt position of the real hidden hand towards the RH (proprioceptive drift). This illusion does not occur when the RH is stroked asynchronously with respect to the participant's own hand (see Chapter 3 for a more detailed description). It has been proposed that RHI causes a multisensory conflict between touch, vision and proprioception, which is resolved by the brain through the instauration of the illusion: the felt tactile sensation (from the real hidden hand) is coherently perceived coming from the location in which is seen (over the RH). Interestingly, the prevalence of the illusion over time (Botvinick and Cohen, 1998) and the subjective experience of intensity degree of illusion (Longo et al., 2008) are positively correlated with changes in the position of the real hand felt against the RH (the more illusory experience of ownership the higher the proprioceptive drift). Manipulation of the sense of body ownership during the RHI has been widely replicated (Armel and Ramachandran, 2003; Ehrsson et al.2004; Longo et al, 2008; Tsakiris and Haggard, 2005; Tsakiris et al, 2007; Kammers et al., 2008) and this procedure is well accepted as a tool to investigate the body ownership, since it creates a temporary condition in which an external object becomes part of the subject's body (Tsakiris, 2010).
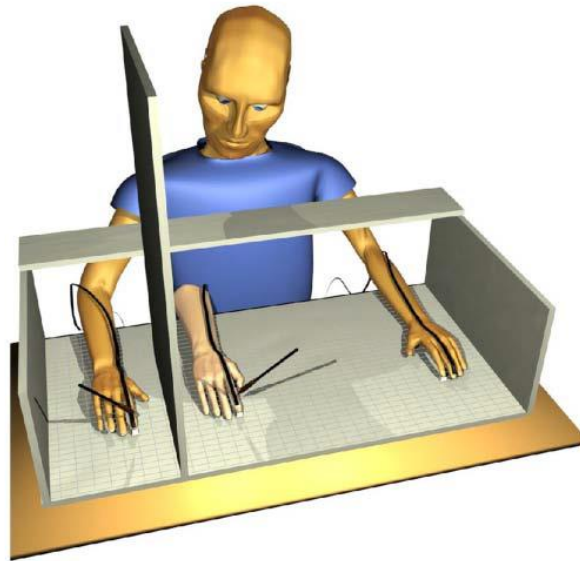
FIG. 1.3. A canonical setup to elicit the rubber hand illusion. (Image and caption adopted from Kammers et al., 2008).

However, intermodal matching *per se* is not sufficient to elicit the illusion; physical and postural similarities of the RH with the real hand constrain the integration between vision and touch, i.e. the RH must be positioned in an anatomically correct position with respect to the shoulder and the body image (Tsakiris and Haggard, 2005; Costantini and Haggard, 2007). Haggard and colleagues manipulated posture (congruent with egocentric coordinates or not) of the viewed RH and identity of the viewed object (RH vs wooden stick) and found that RHI occurred only when the RH was in a congruent posture or of a congruent identity with respect to the participant's hand. Moreover, incongruent RH posture and identity, and neutral objects did not elicit proprioceptive drifts. According with the body gestalts, the RHI occurred only when participants viewed a congruent RH that was stimulated synchronously with their own hand. The authors concluded that the anatomical and postural correspondence between the *part of the body* visually stimulated (RH) and the one tactile stimulated (real hidden hand) is a necessary condition for the emergence of ownership over the RH (Tsakiris and Haggard, 2005; Costantini and Haggard, 2007). Other experimental evidences

confirm that RHI is not induced when a non-corporeal object, such as a wooden stick, replaces the

RH (Tsakiris et al, 2008; Armel and Ramachandran, 2003). In sum, during the RHI, two main

component of the embodiment of the RH are successfully influenced: the sense of ownership over

the RH and the bias in the perceived position of the participant' real hand. Which are the

mechanisms on which this phenomenon relies? It has been proposed that the embodiment process

depends on a combined bottom-up match between visual stimulation of the RH and tactile

stimulation of the subject's hidden hand (Botvinick and Cohen, 1998; Tsakiris, 2010). Furthermore,

the incorporation depends on the corresponding match between visual image of the RH and current

representations that the subject has of his own body, consisting of at least one body schema

(proprioceptive) and one body image (visual) (Tsakiris, 2010). These last matching processes may be

called top-down, since they depend on an internal mental representation rather than by a current

of afferent sensory input. At this point we should try to describe what changes in the subjects' bodily

experience during the RHI. One possibility is that the RH is simply added as a third limb, with no real

impact on the experience of our own hands. Alternatively, the rubber hand can "really" *replace* the

hand of the participant and, in turn, alter his/her body experience (Tsakiris, 2010). Subjective reports

and behavioral observations suggest that the rubber hand is not simply added as a third part, but

instead replaces the real hand, both in terms of phenomenal experience and physiological regulation

(Tsakiris, 2010). In a study proposing a psychometric approach to the body ownership, participants

have denied that they felt like they had three hands, while they openly expressed that they felt as if

their own hand had *disappeared* (Longo et al., 2008). Furthermore, subjects showed stronger skin

conductance reactions when the fake arm was "injured" after synchronous stimulation compared to

asynchronous stimulation (Armel and Ramachandran, 2003). Additionally, it has been demonstrated

that self-generated movement produces a different kind of body awareness than purely afferent

signals, so that the active body is experienced as more coherent and unified than the passive body (Gallagher, 2005; Tsakiris et al., 2006). In conclusion, executing an action (whether passively or actively) plays an important role in the sense of ownership and, more in general, in self-bodily consciousness (Tsakiris et al., 2010). This last evidence suggests the idea that the awareness of oneself, as bodily-self, emerges from the experience of oneself as agentive (Gallese & Sinigalia, 2010; 2011). All together these findings suggest that RHI cause a *real incorporation* and *substitution* of the real hand and that sense of ownership results from the localization of the tactile property within a body representation constructed on the basis of the information that is available to the subject (e.g. vision, touch and proprioception for most of the people) (Tsakiris, 2010). So, it is quite clear that without multimodal interaction, the phenomenon of the rubber hand would not have been possible.

Several studies have attempted to identify the neural correlate of RHI experience, using functional magnetic resonance imaging (fMRI) (Ehrsson et al, 2004; Ehrsson et al, 2005). It has been suggested that the embodiment of the RH depends on a correspondence between the "seen" and "felt" of the body part concerned. The ventral premotor cortex (vPM), anatomically connected to visual and somatosensory areas in the posterior parietal cortex and to the frontal motor areas (Rizzolatti et al., 1998; Graziano, 1999; Makin et al., 2008), is a reasonable location where all these different aspects contributing to the RHI could be integrated. Premotor neurons receive information about both the proprioceptive and visual representations of the hand position (Graziano et al., 1994; Lloyd, 2003), and in fact they discharge when the hand is touched or when a visual stimulus is presented near it (Graziano et al., 1994, Rizzolatti et al., 1981; Fogassi et al., 1996). Therefore, it is plausible to assume that the activity of the vPM reflects the detection of congruent multisensory signals related to one's own body parts, which in turn could be responsible for the feeling of body ownership. But, even if

electrophysiological studies show that the position of the limb can be *computed* in this area based on multi-sensory information, they cannot inform us about whether and how its activity is linked to the *conscious experience* of owning a limb. Ehrsson and colleagues (2004) provided the first functional evidence in support of the hypothesis that the feeling to own a body depends on multisensory integration processes (Figure 1.4), showing an increased activation in the left premotor cortex after the subjects indicated that the illusion had begun. Furthermore, there was a linear correlation between the subjective evaluation of illusion (questionnaire rating) and the level of neural activity in the vPM cortex. These results support the hypothesis that neural activity in these regions is correlated with the emergence of the feeling to own a body-part and provides evidence to believe that activity in this area is deeply associated with the subjective experience that the body one sees belongs to oneself (Ehrsson et al, 2004; Ehrsson et al, 2005; Berti et al., 2005; Arzy et al., 2006). However, the conscious experience to own a body is a high-order experience which goes beyond the functionality of a single area, but relies on the whole system. In fact, before the illusion began, it has also been found increased levels of activity in extra-striate areas, in the bilateral intraparietal cortex, in bilateral dorsal premotor cortex and supplementary motor area, as well as the left side of the cerebellum, in the left putamen, and in the left ventral thalamic nucleus (Ehrsson et al, 2004; Ehrsson et al, 2005). Furthermore, a significant relationship between the activity of the right side of the cerebellum and the strength of the illusion was described (Ehrsson et al, 2004; Ehrsson et al, 2005). This evidences suggest that a great number of cerebral motor network are relevant in the emergence of the conscious experience to own an active body; in light of these findings, the premotor cortex, given its anatomy-functional properties, instead of the *hot spot*, could be conceptualized as a very relevant site of a wider and distributed sensory-motor system, of which

all the component, at different level of complexity, contribute with the emergence of body ownership.
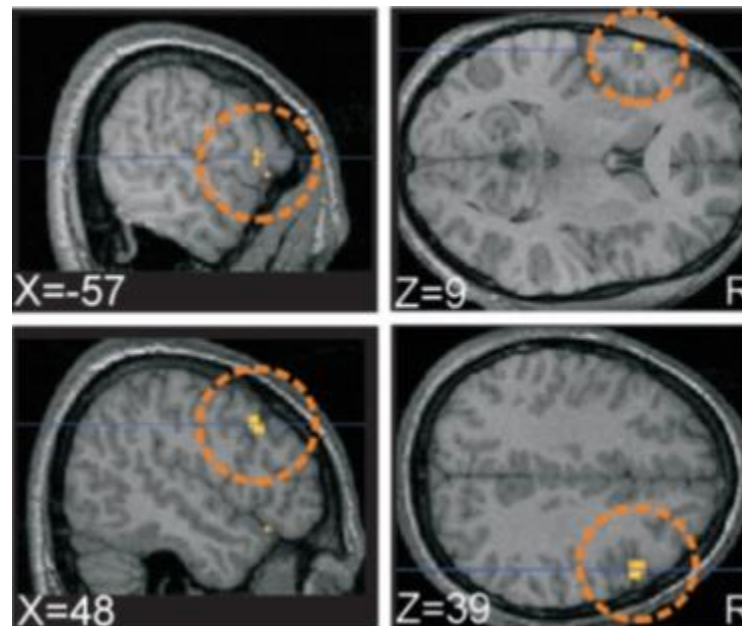
FIG 1.4. Bilateral premotor activity that reflects the rubber hand illusion. The activation peaks are located in the inferior part of the precentral sulcus. R denotes right; coordinates in standard space are indicated at lower left. (Image and caption adopted from Ehrsson et al., 2004).

We saw that impairment of the network implicated in multisensory integration could reflect in body ownership disorder (Garcin et al, 1938; Gerstmann, 1942; Vallar and Ronchi, 2009; Romano et al., 2014; Gandola et al., 2012; Karnath et al., 2010; Critcley, 1974; Moro et al., 2004; Loetscher et al., 2006; Brugger et al., 2013; Hilti et al., 2013). Moreover, in most of those cases (except for xenomelia, in which primary sensory-motor functionality seems spared), patients always suffered of primary sensory-motor deficit (hemeplegia and/or hemianestisia), suggesting that a normal functioning of those brain areas is a necessary condition to experience our body as owned by us. At the same time,

during the RHI, a similar phenomenon has been described: subjects report a feeling of dis-ownership over the deluded hand (Longo, 2008) and it has been shown that skin temperature of the real hand decreases when they take ownership of an artificial counterpart (Moosley et al., 2008; Kammers et al., 2012; Rohde et al., 2013). The recorded drop in skin temperature is the first physiological correlate of the RHI and supports the idea that conscious sense self, and physiological regulation of the physical self are mutually linked.

This and other similar evidence is starting to suggest that body awareness and more in general of self-awareness, are built on the continuous sensory-motor interaction between self and the environment (Merleau-Ponty, 1962; Varela, 2000; Gallese & Sinigaglia, 2011) and on the activity of multisensory brain areas (Ehrsson et al., 2004; 2005; Blanke et al., 2015). In other words, representations of the body continuously interact with sense of agency, allowing human beings to experience themselves as agent on the basis of the congruence between self-generated movements and their expected consequences (Tsakiris et al., 2007; Gallese & Sinigaglia 2010; 2011; Gallagher & Zahavi, 2009; Jeannerod, 2007). Nevertheless, the contribution of sensory-motor system in generating the body ownership is still not completely understood.

In Chapter 3, we directly address this issue by asking whether and how the subjective and sometime illusory sense of body ownership interacts with objective measures of the sensory-motor system. We combined the RHI paradigm with transcranial magnetic stimulation (TMS) in order to study the interaction between body awareness and motor control, with the aim of providing a physiological motor counterpart of the body ownership alteration, as that occurring during the RHI. In a sample of healthy subjects, we investigated the modulation of the real hand parameters during RHI from a motor point of view, hypothesizing that a *disembodiment* of the real (deluded) hand during the RHI

might be measurable as a decrease in readiness to move the hand, reflected in a lower excitability of its motor pathways. During Experiment 1, subjects were tested in two visual-tactile stimulation conditions: synchronous and asynchronous. MEPs were elicited by a TMS single-pulse of the hand area in the left primary motor cortex (M1) and recorded from the first dorsal interosseous muscle (FDI) of the right hand. In Experiment 2 (control) we replicated the same procedure, but recording from the left FDI, in order to verify that the physiological modulation was specific for the hand subject to the RHI. Behavioral results showed the expected well described effect of the RHI in the synchronous compared to the asynchronous condition (feeling of ownership towards the RH, feeling of dis-ownership towards the deluded hand, proprioceptive drift towards the RH). Physiological results showed a decrease in MEP amplitude in the synchronous condition (in which subjects experienced the illusion), while MEPs in the asynchronous condition were of comparable amplitude to MEPs recorded in the baseline. This study provides the first physiological evidence that the feeling of disembodiment of the real hand during the RHI is accompanied by a significant drop in motor excitability recorded in M1. These results contribute to the theoretical understanding of the link between body awareness and movement, suggesting that motor readiness and sense of body ownership are strongly linked, i.e. that bodily awareness depends on the possibility of movement.

Chapter 2

When your arm becomes mine: Pathological embodiment of alien limbs using tools modulates

own body representation

2.1 Introduction

When we interact with the world around us, spatial, motor and bodily representations contribute, in different ways, to the conscious experience of the self as an acting body. We can relate this normal bodily experience to the classical concept of "body schema", firstly described by Head and Holmes (1911) as an un-conscious, bottom-up, dynamic representation relying on proprioceptive information from the muscles, joints and skin. Considering the motor nature of body schema, a fundamental issue to be clarified is the relationship between body schema and motor and spatial cognition. Head and Holmes suggested that the nature of body schema is not only sensory-motor but also "action-oriented", in the sense that the possibility of action execution, intrinsic to the body function, can modulate how we represent the spatial extension of our body with respect to the external world (Gallese and Sinigaglia, 2010). Action execution, in turn, takes place in "action space" which can be coded as "near" or "far" relative to the acting body. Near (peripersonal) and far (extrapersonal) space are behaviorally defined as the space within and beyond hand reach, respectively (Berti and Frassinetti, 2000). This definition is based upon both neurophysiological evidence in the monkey and behavioral, PET and TMS evidence in humans showing that near and far space representations in the brain are anatomo-functionally dissociated. In the monkey, near space seems to be represented in frontal area 6 and in the rostral part of the inferior parietal lobe, area 7b and area VIP (Colby et al., 1993), whereas far space is apparently coded in area 8 and area LIP (Colby et al., 1996). Behavioral (Berti and Frassinetti, 2000; Maravita et al., 2003; Farné et al., 2007), PET

(Weiss et al., 2000) and TMS (Lane et al., 2013) studies in humans have confirmed this dissociation. Furthermore, recent findings indicate that near and far space representations are not to be considered as static concepts, but as dynamic entities: for example, active tool-use can reshape one's own body schema, remapping near space to include the tool used to reach for objects located in far space (Maravita and Iriki, 2004, for a review). In the monkey, it has been shown that the area of visual receptive fields (vRFs) of bimodal visuo-tactile parietal neurons (known to map the subject's peripersonal space) can be modified by actions performed with tools (Iriki et al., 1996; Ishibashi et al., 2000). Indeed, the vRFs anchored to the paw were shown to encompass the entire length of the tool used to reach food located in far space, as if the tool held by the animal's hand were incorporated into the body schema. A number of studies in humans – both in brain-damaged and in healthy participants – have shown similar changes following practice to reach far visual stimuli with a tool. It has been shown that reaching with a tool a far ipsilesional target may increase the saliency of that stimulus so as to increase extinction of a contralesional tactile stimulus in patients affected by cross-modal extinction (di Pellegrino et al., 1997; see also Farnè and Ladavas, 2000; Farnè et al., 2005). Several line-bisection studies on patients with selective neglect for near or for far space indicated that tool use can reduce or increase neglect according to the sector of space within or outside reaching distance where the lines are positioned (Ackroyd et al., 2002; Berti and Frassinetti, 2000; Neppi-Mòdona et al., 2007; Pegna et al., 2001). Interestingly, such a dynamical spatial remapping was modulated not only by visual and somatosensory feedbacks, but also by the modality of execution. For example, if the context required a pointing action (usually executed in far space), a far space representation was activated; if the context required a reaching action (usually executed in near space), near space was activated irrespective of the absolute spatial position of the object. Note that in this case the extension of body schema was modulated by the intentional action

executed. In healthy subjects, it has been shown that the progressive increase in line bisection errors with increasing stimulus distance was abolished if participants used, instead of a laser pointer, a long stick to reach objects in far space (Longo and Luorenco, 2006). It has been also documented that tool-use may increase the impact of a visual distractor on tactile discrimination (Holmes et al., 2008; Maravita et al., 2002a, 2002b). More importantly for the present study, a number of studies suggested that the modulatory effect of tool-use in space coding may be accompanied by a parallel change in the representations of body metrics (e.g., Bonifazi et al., 2007; Farné et al., 2007; Maravita and Driver, 2004). This hypothesis has been confirmed in a recent study (Sposito et al., 2012) showing that, in healthy subjects, active tool-use modulates the representation of related body parts; i.e. after tool-use training, participants showed an increased representation of the length of the arm handling the tool. Taken together, these findings indicate a relationship between body schema, action execution and space representation and that body schema is better conceptualized as the neurocognitive result of implicit sensory monitoring for action in a dynamic space. Although viewed as an unconscious representation, body schema is tightly linked to the representation of both intentional processes and spatial coding, contributing in fundamental ways to the emergence of the conscious experience of the self as an acting body in the space. A normal interaction with the world implies the implicit notion that the body executing actions in the space is mine (not yours, not others), i.e. it implies a normal sense of body ownership. But what happens when the sense of body ownership is dramatically altered as, for instance, after a brain damage? In brain-damaged patients with motor and somatosensory impairments, body awareness can be pathologically altered. In some cases, patients may feel a sense of strangeness towards their contralesional limbs felt as separated from their own body. The more frequent manifestation of this disorder is characterized by a sense of disownership, which is the delusional belief that the contralesional limbs do not belong to one's

own body but to another person (a disturbance called somatoparaphrenia: Vallar and Ronchi, 2009; Gandola et al., 2012; Romano et al., 2014). The possibility of the existence of an opposite behavior, i.e. patients who misidentify other people's limbs as their own, has been rarely considered. However, in recent studies (Garbarini et al., 2013a, 2014; Garbarini and Pia, 2013; Pia et al., 2013a), this behavior has been observed in a sample of patients, who, while not explicitly denying that their contralesional (left) limbs belonged to themselves (as in the somatoparaphrenic delusion of disownership), claimed that the examiner's left hand was their own whenever it was positioned, in egocentric coordinates, next to their left hand. This delusion of ownership, which we called "pathological embodiment", although resembling the "rubber-hand-illusion" (Botvinick and Cohen, 1998), was spontaneous and not induced by any experimental procedure. Patients treated and cared for the experimenter's left arm as if it was their own, showing a consistent embodiment of the alien hand in their own body schema (because of this behavior, we named them "E+" patients). Interestingly, this phenomenon occurs only when the alien hand is located in a position coherent with the patients' higher-order and pre-existing body representation. It is important to consider that in E+ patients the pathological embodiment occurs only when the alien arm is in egocentric coordinates and it is aligned with the patients' contralesional shoulder, exactly where it is expected to be. If the position of the alien arm is misaligned with respect to the patient's shoulder, the pathological embodiment does not occur and patients correctly discriminate their own arm/hand from the alien arm/hand (see Section 2.2.2.2 for details of how the embodiment is evaluated). Previous studies stressed the crucial role of the alignment of the alien arm with the shoulder in determining embodiment phenomena during the rubber hand illusion. Pavani et al. (2000) have shown that the illusion effect disappears when the fake hand is misaligned with respect to the subject's shoulder (see also Costantini and Haggard 2007, where stimulation and posture of both the

real and the fake hand were manipulated, and Lloyd (2007), where the effect of proximity between the fake and the real hand was investigated). Accordingly, Farnè et al. (2007) described, in right-brain damaged patients, a left tactile extinction following visual stimulation of a right rubber hand. Interestingly, this cross-modal extinction was only evident when the rubber hand was aligned with the patients' shoulder; on the contrary, when the rubber hand was misaligned with respect to the patients' shoulder, cross-modal extinction was strongly reduced. Critically for the present study, the pathological embodiment occurs not only with a static alien hand, but also with a moving hand: when the examiner moved his/her left hand, patients, to their surprise, claimed that they were moving their own (paralyzed) hand. Previous studies demonstrated that this phenomenon is not a mere verbal confabulation, but reflects a powerful cognitive mechanism capable of altering the patients' motor and somatosensory functions. For example, in the motor domain, these patients showed significant interference effects of the alien arm movements on the actual movements of their own intact arm (Garbarini et al., 2013a). In the somatosensory domain, when painful stimuli were delivered to the alien embodied hand, patients referred to feel pain on it (Pia et al., 2013a) and showed coherent physiological reactions, as if the own hand was stimulated (Garbarini et al., 2014). In the present study we asked whether an altered sense of body ownership, as that shown in the delusional embodiment of alien body parts described above, can modulate both intentional motor processes and the spatial extension of the own body representation. As already mentioned, previous evidence in normal subjects has demonstrated that active tool-use modulates the representation of related body parts. It has been shown that participants estimate the mid-point of their forearm to be more distally located after a 15 min training with a 60 cm long tool, as compared to a pre training condition (Sposito et al., 2012). Here, we investigated the effects of the observation of an alien arm performing a tool-use training on the length representation of the own forearm, in both healthy

subjects (Experiment 1) and in brain-damaged hemiplegic patients with a pathological embodiment of the alien arm using the tool (Experiment 2). Healthy subjects were tested in two different conditions, where they were asked a) to actually perform the tool-use training with their own arm (Action condition) or b) to observe an alien arm (the examiner's one) performing the tool-use training, while holding (Observation with-tool condition) or not (Observation without-tool condition) a similar tool (see details in Section 2.2.1). According to Sposito et al. (2012), we expected to find an overestimation of the forearm length only after active tool-use training (Action condition). We were also interested in verifying if this overestimation effect could be induced by simply observing an alien arm performing the tool-use training. According to Costantini et al. (2011), a difference between the observation with-tool and without-tool conditions could be expected. Indeed, these authors found that observing tool actions may extend the representation of reaching space only when observers shared the same action potentialities with the agent, i.e. while holding a tool compatible with the goal and the spatial range of the observed action. As far as patients are concerned, in our experiment they were asked to try to perform the tool-use training with their own (paralyzed) limb, while the alien arm performed the tool-use training acting either in the E+ position, where the pathological embodiment systematically occurs, or in the E- position, where the embodiment does not occur (see details in Section 2.2.2.2). The crucial aspect of this experiment is that, although the task implied the observation of an alien arm performing the training (as in the Observation conditions of Experiment 1 with normal subjects), it was proposed as an active task, where hemiplegic patients were asked to try to perform the required movements with their plegic arm (see details in Section 2.2.2.3). On the basis of data from previous studies, in the E+ condition, we expected patients to truly believe to be actually performing the task with their own arm and, consequently, to show an overestimation of their forearm length in the post-training phase with respect to the pre-training phase (similarly to

healthy subjects actually performing the task in the active condition). Conversely, in the E- condition, we expected patients to be aware of not performing the task with their own arm and, hence, to show different results at the bisection task. If these predictions were confirmed, this would strongly support the view that the sense of body ownership not only extends to intentional motor processes but also modulates the sensory map of action-related body parts.

2.2. Materials and methods

2.2.1. Experiment 1

2.2.1.1. Participants

Twenty right-handed healthy volunteers (8 females and 12 males), 57-90 years of age (mean 70.5 ± 10.6), matched for age and educational level with the sample of brain-damaged patients involved in the second experiment (see Section 2.2.1), were recruited for the experiment. None of the subjects had a history of psychiatric or neurological disorders. All participants gave their written informed consent before taking part to the experimental procedure, which was approved by the ethical committee of the University of Turin, in accordance with the Declaration of Helsinki. Participants were all naive to the experimental procedure and to the aims of the study.

2.2.1.2. Experimental design

We employed a between-subject experimental design, with a unique "Action condition" and two different "Observation conditions" ("With-tool" and "Without-tool"), performed by two samples of 10 subjects each. All participants in the Action condition performed a tool-use training with their own arm. On the contrary, during the Observation condition participants had to stay still and observe the examiner's arm perform the tool-use training: half of the subjects held a similar tool in their hand (Observation With-tool condition); the other half did not hold any tool (Observation Without-tool condition). The Action and the Observation conditions were performed in two different experimental sessions, spaced one week from each other. Half of the participants started with the Action condition and the other half with the Observation condition. See details in Fig. 1A and B.
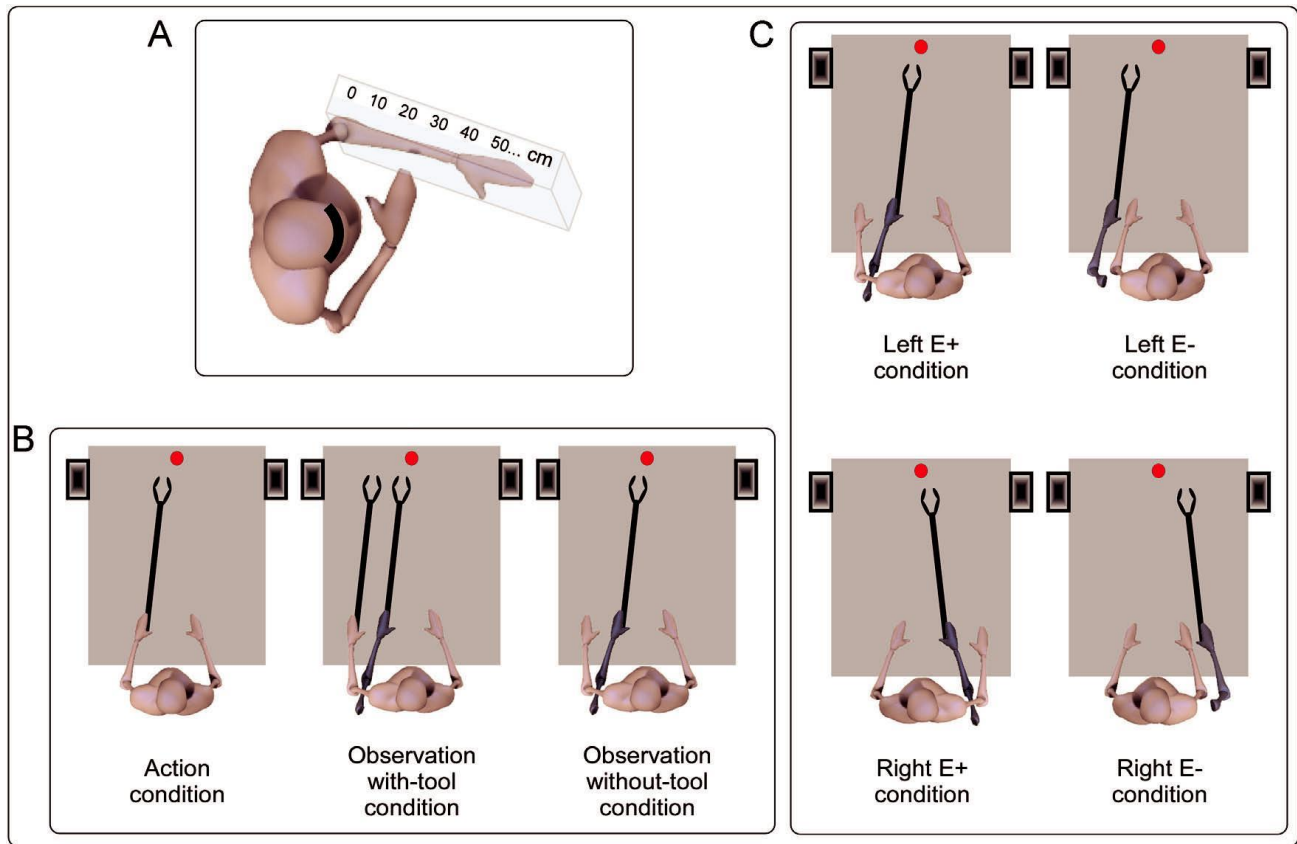
2.2.1.3. Experimental procedure

The experiment comprised three phases. Firstly, participants were blindfolded and asked to perform a forearm bisection task in which they had to estimate, by means of 15 pointing movements, the mid-point of their left forearm (pre-training phase). Secondly, they were asked to perform 15 min of tool-use training (in free viewing). Finally, at the end of training, they were blindfolded and asked to perform again the forearm bisection task (post-training phase). All participants performed the forearm bisection task with the right arm and the training task with the left arm (according to the literature, the effects of training are equally present on the dominant and on the non-dominant arm; Sposito et al., 2012). When we designed the Experiment 1, we chose to train the left arm because we were interested in matching the healthy subjects' performance with that of E+ patients (Experiment 2), more frequently showing a pathological embodiment for the left side of the body. Given the fact that, in the Experiment 2, we recruited also one left brain-damaged patient showing a right limb embodiment, following the suggestion of an anonymous reviewer, we additionally tested 10 right-handed age-matched healthy subjects (5 females and 5 males; 54 - 85 years of age (mean 68.5 ± 9.3), per-forming the active tool-use training with the right hand. The forearm bisection task and the tool-use training are de-scribed in detail as follows.

Forearm bisection task. Blindfolded participants were instructed to indicate, by using their right/left index finger, the midpoint of their left/right distal upper limb segment comprising the forearm and the hand, considering the elbow and the tip of the middle finger as the two extremities. During the task, the forearm was kept in a radial posture and placed inside a Plexiglas parallelepiped (70x10x11 cm^3), in order to prevent any possible tactile feedback from the bisections. On the top of the screen above the arm was glued a paper rule with the 0-cm scale index in correspondence of the elbow, in

order to easily measure the position of the subjective midpoint (p). Then, in order to obtain a percentage score relative to each participant's subjective arm length, we used the following formula: [(p/arm length) 100]. The task was not a time trial and on-line corrections were not allowed. Each participant performed a total of 30 bisection pointing, 15 before (Pre-training) and 15 after tool-use training (Post-training) (Sposito et al., 2012). See details in Fig. 1A.

Tool use training. All participants performed the task sitting at a table. In the Action condition, they were instructed to retrieve a number of targets by means of a garbage plier (70-cm long) and put them, according to the examiner's instructions, in one of two boxes located along the right or the left side of the table. It is important to note that only distal movements were required during the training phase for triggering the plier lever with the left hand and for orienting the wrist to the left or to the right in order to grasp targets and to put them in the requested box. Targets were different from each other by color (i.e. red, yellow, blue, green), shape (i.e. circle, cube, parallelepiped) and dimension (i.e. big or small). In the Observation condition, participants were instructed to stay still and to observe the examiner's left arm (in dark gray in Fig. 1B) performing the tool-use training with the garbage plier. They were specifically asked to focus their attention on the action performed by the examiner, orienting their gaze to the left or to the right, according to the location of the box where the examiner put the objects. The alien arm was located in a proximal position with respect to the participant's trunk midline. According to the group membership, participants were handling or not a garbage plier identical to that used by the examiner (Observation With-tool and Observation Without-tool conditions, respectively). See details in Fig. 1B.

FIG. 1. Experimental task. (A) Bisection task: schematic aerial view of the experimental setting depicting the forearm bisection procedure in Experiments 1 and 2; the subject's arm lied inside a translucid plexiglas parallelepiped to avoid tactile feedback. The numbers on top represent the paper ruler used to calculate the subjective midpoint in cm (see Section 2.1.3 for details). (B) Tool-use training, Experiment 1: Healthy volunteers performed the training either with their own arm (Action condition) or observing the examiner's arm (the dark gray one) perform the task, handling (observation with-tool condition) or not (observation without-tool condition) a similar tool. (C) Tool-use training, Experiment 2: with patients the training was performed by the examiner's (alien) arm (in dark gray). The alien arm could act (a) in a position more proximal to the patient's trunk midline (E+ condition, upper left and right quadrants), where embodiment occurs, or (b) in a more distal position (E condition, lower left and right quadrants), where embodiment does not occur and patients correctly acknowledge that the alien arm belongs to the examiner. The task was performed on the patients' contralesional side.

2.2.1.4. Data analysis

In Experiment 1, the mean forearm bisection value of healthy subjects (n=20) was used as dependent variable. These data were entered in a 2*2*2 repeated measures ANOVA with "tool" (two levels: "with-tool" and "without-tool") as between subject factor and "condition" (two levels: "action" and "observation") and "training" (two levels: "pre" and "post") as within subject factors. Planned comparisons were performed in order to compute the contrasts of interest. Given the fact that the adopted design could potentially introduce more noise in the observation conditions (where 10 subjects performed the with-tool task and the other 10 the without-tool task) than in the action condition (where all 20 subjects performed the same task), we checked for the equivalence of variance of the active condition either vs the observation-with-tool and the observation-without-tool condition by means of F-tests for the equivalence of variance. The F-tests were not significant (Active vs Observation-with-tool: p=0.63; Active vs Observation-without-tool: p=0.11), suggesting that the equivalence of variance can be assumed and the ANOVA run properly. As suggested by an anonymous reviewer, we also run an additional ANOVA to directly test the contrast Observation-with-tool against the Observation-without-tool, ruling out the possible confound of active tool use. Finally, to compare the left-hand training vs the right-hand training, we performed a 2*2 ANOVA with "side" (two levels: "left" and "right") as between-subject factor and "training" (two levels: "pre" and "post") as within subject factor. The mean forearm bisection value of healthy subjects performing the left hand training (n=20) and the right-hand training (n=10) was used as dependent variable. The equivalence of variance of the left-hand training (n=20) vs the right-hand training (n=10) was checked by means of F-tests. The F-tests were not significant (p=0.43), suggesting that the equivalence of variance can be assumed and the ANOVA run properly.

2.2.2. Experiment 2

2.2.2.1. Participants

Four brain-damaged patients of cerebrovascular origin were recruited at the "San Camillo" Hospital (Turin, Italy). All participants gave their written informed consent before taking part to the experimental procedure, which was approved by the ethical committee of the ASL TO 1 of Turin and in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194). Patients were all naive to the experimental procedure and to the purpose of the study. They were all assessed using the following tests: general cognitive tests (Montreal Cognitive Assessment – MOCA or Mini Mental State Evaluation – MMSE); visual field exam; assessment of hemiplegia, assessment of anosognosia for hemiplegia, assessment of hemianesthesia; tests for extrapersonal neglect (Behavioral Inattention Test – BIT – conventional and behavioral subtests; DILLER) and for personal neglect (FLUFF). Patients were also evaluated for somatoparaphrenia (Fotopoulou et al., 2011). Exclusion criteria were: (1) previous neurological or psychiatric history; (2) severe general cognitive impairment (patients under the MMSE cut off or the MOCA cut off were excluded); 3) visual field deficit (patients with visual field scores higher than zero were excluded). See Table 1 for details.

Table 1. Patients' demographic and clinical data.

Patient	E+1	E+2	E+3	E+4
Age	50	65	72	48
Sex	F	M	M	M
Education	5	17	8	5
Etiology	I	I	I	H
Lesion side	LH	RH	RH	RH
Months from onset	6	3	2	2
Visual field defect	0-0	0-0	0-0	0-0
Hemiplegia (HP)	3	2	3	3
Anosognosia for HP	0	0	0	0
Hemianesthesia (HAE)	3	1	2	3
General cognitive impairment	-	-	-	-
Extrapersonal neglect	+		+	+
Personal neglect	-	-	-	-
Somatoparaphrenia	-	-	-	-

Tab. 1. Presence of embodiment (E+) of the experimenter's arm. Sex: M=Male, F=Female. Education: years of school. Etiology: H=hemorrhage; I=ischemia. Lesion Side: RH=Right Hemisphere; LH=Left Hemisphere. Months from onset: number of months between the onset of the disease and the first assessment. For visual field defect (the two values refer to the upper and lower visual quadrants, respectively), hemiplegia, anosognosia for hemiplegia and hemianesthesia scores were ranged from normal (0) to severe defects (3) (Spinazzola et al., 2008, in press; Pia et al., 2014). General cognitive impairment (- = no deficit; + = presence of deficit): MOCA cut off ≥ 14.5/30; MMSE cut off ≥ 24/30. Extrapersonal neglect (- = no deficit; + = presence of deficit): BIT, conventional subtests cut-off ≥ 129/ 146; BIT behavioral subtest cut-off ≥ 67/81; DILLER cut-off omissions l – r ≥ 5. Personal neglect (- = no deficit; + = presence of deficit): FLUFF cut off omissions L ≤ 2. The presence/absence of somatoparaphrenia was evaluated according to Fotopoulou et al. (2011).

Patients were admitted to the study if they showed: a) contralesional upper limb hemiplegia, as reported by the responsible neurologist and confirmed by a motor impairment examination carried out according to a clinical protocol (Spinazzola et al., 2008; 2014; Pia et al., in press), with the score ranking from 0 to 3 (only patients with a score ≥2 were admitted); b) pathological embodiment of an alien arm (E+ patients) (Garbarini et al., 2013a, 2014; Pia et al., 2013a). Patients were classified as E+ according to the pathological embodiment evaluation (see details below, Section 2.2.2.2).

According to this evaluation, we recruited three right-brain-damaged patients (RBD) showing left-limb-embodiment and one left-brain-damaged patient (LBD) showing right-limb-embodiment. Patients" lesion locations were identified through MRI or CT scans. Lesions were mapped onto the MNI stereotactic space with standard MRI volume (voxels of 1 mm^3) through a computerized technique. Image manipulations were obtained with the software MRIcron (Rorden and Brett, 2000). Firstly, the MNI template was rotated on coronal, sagittal and horizontal planes according to the patient's scan angle. Secondly, a skilled rater (LP), manually mapped the lesion onto each correspondent template slice, whereas a second skilled rater (CF) double-checked for the accuracy of the tracings for each patient (in case of disagreement, an intersection lesion map was used – this occurred only once). Thirdly, the maps were back rotated into the standard space. Grey matter involvement was obtained by superimposing the Anatomical Labelling map template AAL (Tzourio-Mazoyer et al., 2002) and the JHU-white matter template (Hua et al., 2008) which categorize the distributions of digital images onto stereotactic space. Patients" brain lesions locations are consistent with those de-scribed in previous studies (Garbarini et al., 2013a; 2014; Pia et al., 2013a). The involved brain structures are shown in Figure 2.
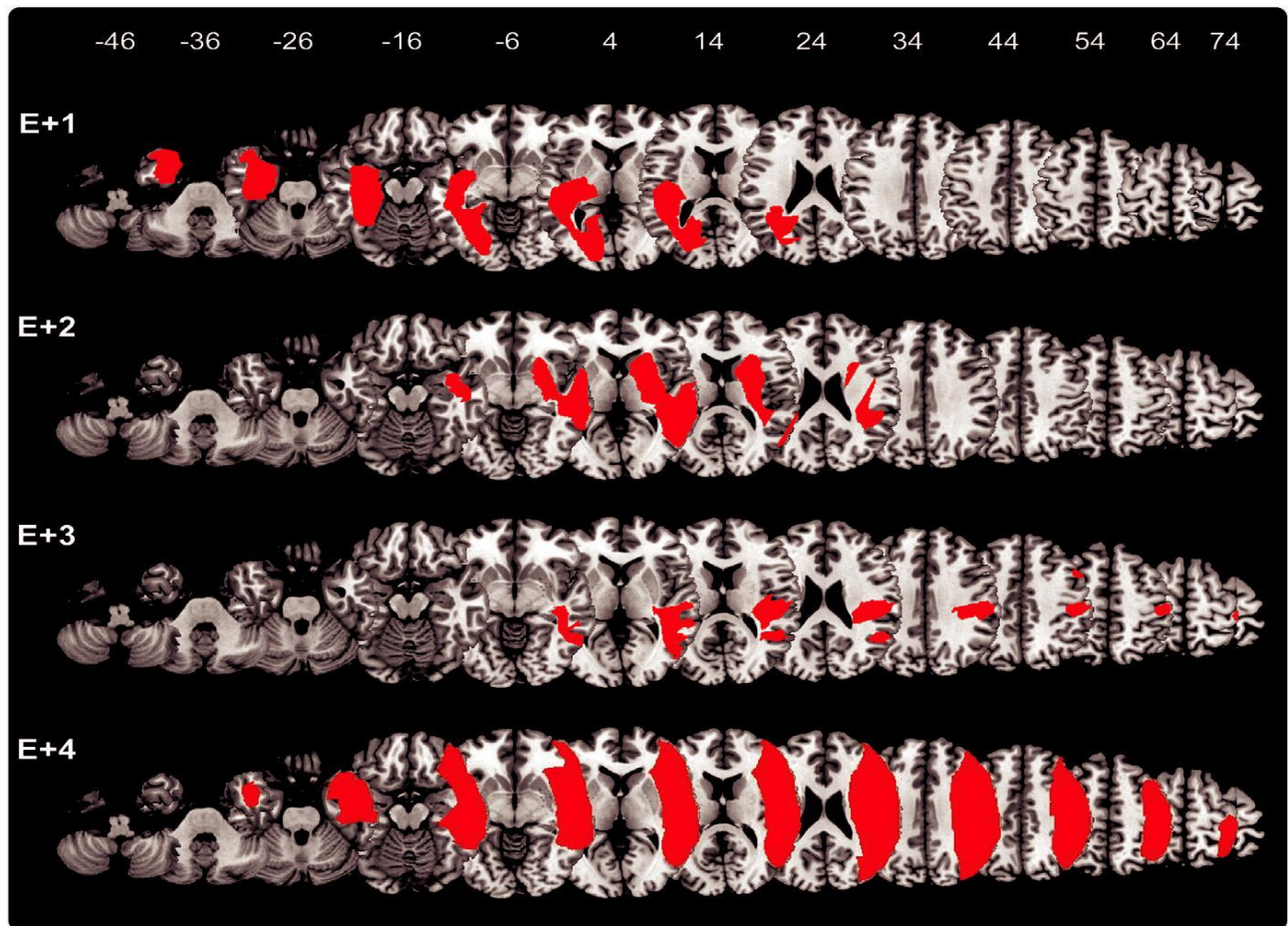
Fig. 2. Patients' lesion reconstruction. E+1. Left-hemisphere lesions, involving: hippocampus, amygdala, middle temporal pole, parahippocampal gyrus, fusiform gyrus, heschl's gyrus, temporo-parietal periventricular white matter. E+2. Right-hemisphere lesions, involving: superior longitudinal fasciculus, anterior limb of internal capsule, external capsule, putamen, globus pallidus, fronto-parietal periventricular white matter. E+3. Right-hemisphere lesions, involving: supramarginal gyrus, middle temporal pole, heschl's gyrus, uncinate fasciculus, cingulum (hippocampus), posterior thalamus, retrolenticular part of internal capsule, putamen, sagittal stratum and temporo-parietal periventricular white matter. E+4. Right-hemisphere lesions, involving: precentral gyrus, inferior frontal operculum, inferior frontal gyrus (triangular part), inferior frontal gyrus (orbital part), rolandic operculum, insula, postcentral gyrus, supramarginal gyrus, angular gyrus, heschl's gyrus, superior temporal gyrus, temporal pole (superior part), middle temporal gyrus. fronto-temporo-parietal periventricular white matter.

2.2.2.2. Embodiment evaluation

In order to include in the study only E+ patients, we tested them with an ad hoc protocol devised to diagnose the presence/ absence of embodiment (Garbarini et al., 2013a; 2014; Pia et al., 2013a). Patients sat on a chair with both hands lying on the table. According to the patient's embodiment side (left or right, de-pending on the damaged hemisphere, right or left, respectively), an alien left/right hand (the examiner's one) was positioned on the table next on the patient's hand in four different positions (see Fig. 3 A D). Note that the distance between the own and the alien hand was always the same (about 10 cm) in all conditions. The difference between conditions were: (1) the frame of reference of the alien hand position (egocentric in A, B and D and allocentric in C); (2) the alien hand-shoulder configuration (aligned with the patient's shoulder in A, C and D; misaligned in B); the alien hand body-side location (ipsilesional intact side in D; contralesional affected side in A, B and C). Prior to the beginning of the experiment, patients underwent 3 simple tests to assess their compliance with task demands and presence or absence of the embodiment phenomenon in that specific time. A white sheet of tissue was used to cover the patient's and the examiner's arms leaving the hands visible and three cubes of different colors (red, blue and green) were placed on the table. Patients were asked (1) to count how many hands and objects were on the table; (2) to reach their paralyzed hand with their intact hand and (3) to name the color of the cube positioned in front of their own hand. In order to start the experiment, a patient had to be errorless in test 1, i.e. identify the three objects and the three hands on the table. Note that in the Embodiment condition (A), E+ the patient fail test 2, i.e. reach the alien hand instead of his/her own hand and test 3, i.e. name the color of the cube in front of the alien hand instead of naming the color of the cube in front of his/her own hand. In the control conditions (B and C), as well as on the intact (ipsilesional) body side (D), the

pathological embodiment should not occur and all the patients should correctly reach/identify their own hand (see details in Fig. 3).
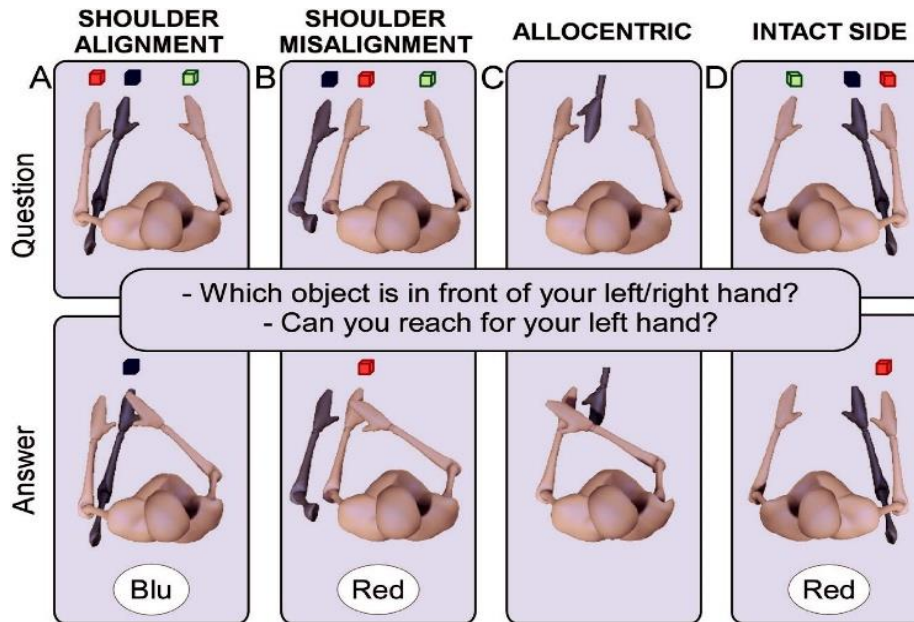
Fig. 3. Embodiment evaluation. An alien left/right arm (the examiner's one) was positioned on the table in four different conditions: (A) The alien arm (in grey) is aligned with the patient's contralesional shoulder, in a position more proximal to the patient's trunk midline than the own arm (shoulder alignment condition). (B) The alien arm (in grey) is (externally) misaligned with respect to the patient's contralesional shoulder, in a position more distal with respect to the patient's trunk midline than the own arm (shoulder misalignment condition). C) The alien arm (in grey) is placed in a position more proximal to the patient trunk midline (as in A) but in an allocentric position, i.e. facing the patient (allocentric condition). (D) The alien arm (in grey) is aligned with the patient's ipsilesional shoulder, in a position more proximal to the patient's trunk midline than the own arm (intact-side condition). The patient was asked: (1) to count how many hands and objects were on the table; (2) to reach his/her own hemiplegic hand with his/her own non plegic ipsilesional hand and (3) to identify his/her own hand on the basis of the color of the object facing the hand. In all conditions the patient counts three objects (blue, red and green) and three hands (question 1). In (A) (lower part) the patient reaches the alien hand (the grey one) (question 2) and identifies his/ her own hand as the one in front of the blue cube (question 3); in (B) (lower part) the patient correctly reaches his/her own hand (the pink one) (question 2) and identifies it as the one facing the red cube (question 3); in (C) (lower part) the patient correctly reaches his/her own hand (question 2); in (D) (lower part) the patient correctly identifies his/her own hand as the one facing the red cube (question 3). Note that in (D) question 2 was not administered: given the contralesional paralysis, patients could not reach for the intact hand with the affected hand.

2.2.2.3. Experimental procedure

Experiment 2, similarly to Experiment 1, comprised three phases: pre-training forearm-bisection task (15 pointing); tool-use training (15 min.); post-training forearm-bisection task (15 pointing) (see details in Section 2.1.3, Fig. 1A C). Note that both bisection tasks and tool-use training were performed by each patient in his/her contralesional side, where embodiment occurred (i.e. with the right side in E+ patient 1; with the left side in E+ patients 2, 3, 4). Furthermore, unlike healthy subjects, hemiplegic patients could not perform the tool-use training, because of hemiplegia, and they all were aware of their motor deficit; i.e. none of them were anosognosic for hemiplegia (see Table 1). Hence, in both E+ and E conditions, tool-use training was per-formed by the examiner's arm and patients were asked "to try" to use the garbage plier in order to perform the task. See details in Fig. 1C.

2.2.2.4. Ownership evaluation

In order to evaluate the patients" ownership during the task, at the end of the training phase of both E+ and E conditions, we addressed the following questions:

1. Did you perform the task with your left/right hand?
2. How could you perform the task with your left/right hand?

2.2.2.5. Data analysis

In Experiment 2, the mean forearm bisection value of patients (n=4) was used as dependent variable. These data were entered in a 2*2 repeated measures ANOVA with "embodiment" (two levels: "E+" and "E-") and "training" (two levels: "pre" and "post") as within subject factors. Planned comparisons were performed in order to compute the contrasts of interest. Given the small sample size, we also performed a single subject analysis (non-parametric Wilcoxon test, e.g. Garbarini et al., 2013b). Finally, in order to compare the difference in performance be-tween pre- and post-training conditions between each single patient and the control sample, we used Crawford's test (two tailed) (Crawford et al., 2010).

3. Results

3.1. Experiment 1: healthy subjects' forearm bisection task

The ANOVA did not show any significant effect for the be-tween-subjects factor "tool" and for all the interactions with the "tool" factor, as well as for the within-subjects factors "condition" and "training". The only significant interaction was "condition training" ($F_{1,18}$=0.1558; p<0.001). In the Action condition, there was a significant increase of the mean forearm bisection values in the post-training relative to the pre-training phase (Action pre=41.69% ± 77.15 (St.Dev); Action post=45.78% ± 76.9; planned comparison: $F_{1,18}$ =5.061; p=0.038). This means that, after training, subjects relatively overestimated their forearm length (see Fig.4). Conversely, in the Observation condition, no significant difference between pre- and post-training was found (Observation pre =42.7% ± 77.44; Observation post =40.46% ± 79.8; planned comparison: $F_{1,18}$ =3.181; p =0.093). Unexpectedly, a not significant tendency in the opposite direction (i.e. a decrease of the mean bisection values in the

post-respect to the pre-training phase) was apparent (see Fig. 4).The results of the additional ANOVA directly testing the contrast Observation-with-tool vs Observation-without-tool (ruling out the possible confound of the Action condition), show that the presence of the tool in the subject's hand was not a significant factor by itself or in the interaction with the pre/post training measurements.
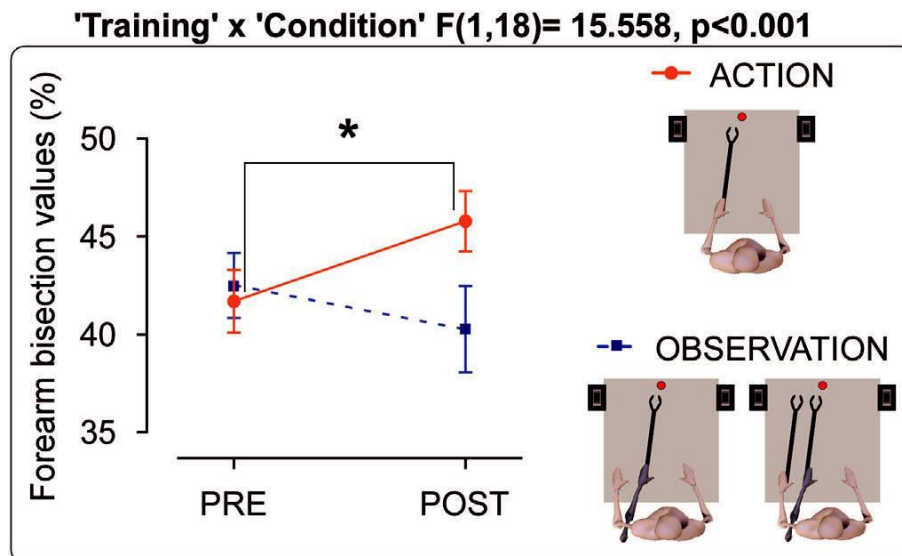
Fig. 4. Results of Experiment 1: Action vs Observation. Graphic representation of normal subjects" (n=20) mean forearm bisection values (in %) in the pre-training (PRE) and in the post-training phase (POST) during the Action (in red, continuous line) and the Observation (in blue, dotted line) conditions. ***p<0.0001; **p<0.001; *p<0.01.

The results of the additional ANOVA directly testing the contrast left-hand training vs right-hand training, show that the be-tween-subject factor "side" is not significant by itself or in the interaction with the pre/post training measurements. The ANOVA found a significant effect of the within-factor "training" ($F_{1,28}$ =10; p<.003), suggesting that in both the left- and right-training there was a significant increase of the mean forearm bisection values in the post- with respect to the pre-training condition (see Fig. 5).
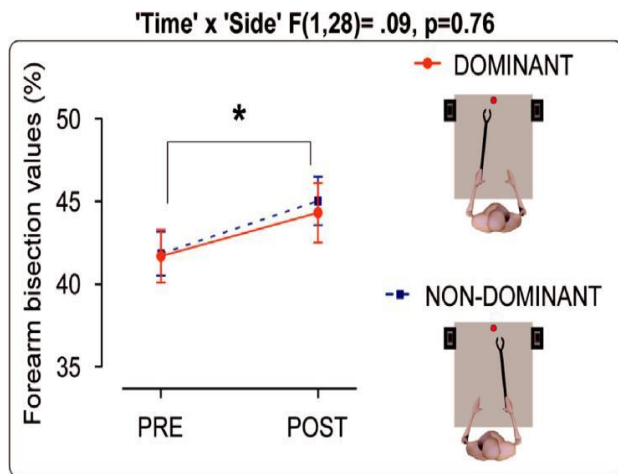
Fig. 5. Results of Experiment 1: Dominant hand vs Non-dominant hand. Graphic representation of the mean forearm bisection values (in %) in normal subjects performing the active tool-use training with the dominant (right) hand (n=10) (in red, continuous line) or with the non-dominant (left) hand (n=20) (in blue, dotted line) in the pre- (PRE) and post-training (POST) conditions. The effect of training is significant (*p<0.01) with no difference between training performed with the left (non- dominant) or right (dominant) hand.
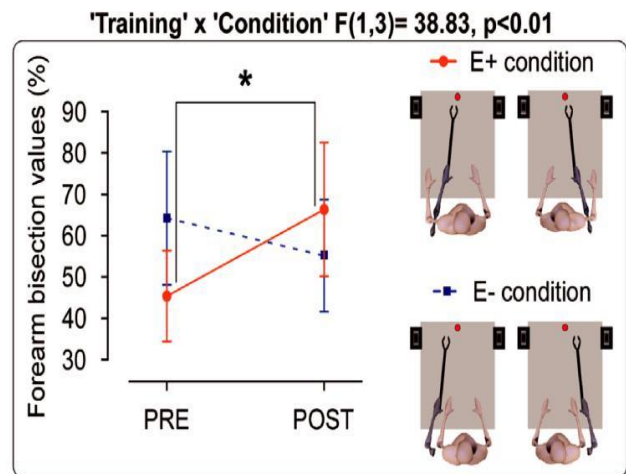
Fig. 6. Results of Experiment 2: E+ condition vs E- condition. Graphic re-presentation of patients' (N=4) mean forearm bisection values (in %) in the pre-training (PRE) and in the post-training phase (POST) during the left/right arm E+ condition (in red, continuous line) and the left/right arm E- condition (in blue, dotted line). *p<0.01.

3.2. Experiment 2

3.2.1. Embodiment evaluation in E+ patients

In the E+ condition, at the end of the training phase, all patients positively answered to the first question (Did you perform the task with your left/right hand?), claiming to have performed the tool-use training with their own (paralyzed) arm. The second question (How could you perform task whit your left/right hand?) produced different answers among patients: E+ 1: "I don't know how I could

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do this… The task was tiring but nice!"; E+ 2: "It's easy to use this plier, only a little movement is enough to trigger the lever… can I try with the other hand?"; E+ 3: "For sure I have done this task with your (the examiner) help…". E+ 4: "I know that you (the examiner) helped me, but I have done it!". An ex-ample is shown in Video 2: E+ 1 patient is filmed while per-forming the tool-use training in the E+ condition and clearly shows that he is convinced to perform the task with her own arm. On the contrary, in the E condition all patients negatively answered to the first question, correctly acknowledging that they did not perform the training with their own arm. Examples are shown in Video Supplementary Materials available online.

3.2.2. E+ patients' forearm bisection task

The ANOVA did not show significant effects for the within-subjects factors "embodiment" and "training", but, more relevant for the purpose of the study, showed significant effects for the interaction "training*embodiment" ($F_{1,3}$ =38.839; p<0.01). In the E+ condition, there was a significant increase of the mean forearm bisection values in the post-training relative to the pre-training phase (E+ pre=45.40% ± 711.03 (St.Dev); E+ post=66.36% ± 716.21; planned comparison: $F_{1,3}$ =30.15; p=0.011). This means that, after training, patients relatively overestimated their forearm length (see Fig. 6). Conversely, in the E- condition, no significant difference between pre- and post-training was found (E pre= 64.27% ± 732.29; E post =55.18% ± 727.06; planned comparison: $F_{1,3}$ =5.18; p=0.1). See Fig. 6.

Single subject analysis revealed that, in the E+ condition, all four patients (similarly to healthy subjects in the Action condition of Experiment 1) showed a significant increase of the bisection values in the post- with respect to the pre-training phase (Wilcoxon tests: E+1: Z=3.29; p<0.001; E+2:

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Z=3.4; p<0.001; E+3: Z=3.4; p<0.001; E +4: Z=3.4; p<0.001), suggesting the presence of a consistent overestimation of forearm length after tool-use when patients were convinced to perform it with their own hand hemiplegic arm. In the E condition, two out of four patients (E+ 1; E+ 2) did not show any difference between pre- and post-training phase; surprisingly, the other two patients showed a significant decrease of the bisection values in the post-respect to the pre-training phase (Wilcoxon test: E+3: Z=3.4; p<0.001; E+4: Z=3.4; p<0.001), suggesting the presence of a relative underestimation effect following the training (similarly to the tendency showed by healthy subjects in the Observation condition of Experiment 1). It is also apparent that, in the pre-training, forearm bisection values in the E condition exceed those found in the E+ condition. To this respect, it must be pointed out that the difference is not significant and it is caused by the performance of 2 patients out of 4 (Wilcoxon test: E+3 $_{E- vs E+:}$ Z=3.4; p=0.00065; E+4$_{E- vs E+:}$ Z=3.4; p=0.00065). As suggested by an anonymous reviewer, we controlled if the ANOVA results (described above) were driven by the above reported difference in baseline values. In an ANCOVA model, where the baseline values were assumed as a covariate, we verified that the crucial interaction "training*embodiment" was still significant ($F_{1,2}$ =33.3; p=0.02), even controlling for the baseline covariate (that was not significant in itself ($F_{1,2}$ =9; p=1). This suggest that the difference in baselines is unlikely to have influenced our findings. The Crawford's test (Crawford et al., 2010) was used to compare the results of each patient, tested in Experiment 2, with the results of healthy subjects in Experiment 1 (see Fig. 7). First, we tested whether the effect of tool-use training (the difference post- minus pre-training bisection values) in the E+ condition was significantly different in patients vs healthy subjects. Crawford's tests (two tailed) revealed that in three out of four patients the effect was significantly greater (E+ 1: Z DCC [difference between case and controls] = 4.826; p=0.0001; E+2: Z DCC= 3.172; p =0.005; E+3: Z DCC= 4.420; p=0.003). Hence, this means that the relative overestimation effect after tool-use is

stronger in patients than in controls. Secondly, we tested whether the effect of tool-use training (the difference post- minus pre-training bisection values) in the E+ condition was significantly different from the effect of the Observation condition in healthy subjects. Crucially, although de facto in the E + condition patients observed an alien arm per-forming the training (similarly to controls in the Observation condition), Crawford's tests (two tailed) found a significant difference between each patient in the E+ condition and controls in the Observation condition (i.e. after tool-use patients over-estimated their forearm length, whereas healthy controls tended to underestimate it) (E+ 1: Z DCC= 4.892; p=0.0001; E+ 2: Z DCC= 3.420; p=0.003; E+ 3: Z DCC= 3.814; p=0.006; E+ 4: Z DCC= 2.483; p=0.03). Finally, we compared the effect of tool use training (the difference post- minus pre-training bisection values) in the E condition, in each patient vs healthy subjects. In two out of four patients (E+ 1; E+ 2) Crawford's tests did not find any significant difference with respect to controls. Patients E+ 3 and 4, instead, showed a relative underestimation effect of their forearm length stronger than that found in healthy subjects (E+ 3: Z DCC=5.384; p=0.007; E+ 4: Z DCC=3.862; p=0.003). We also performed Crawford tests in order to compare the pre-training bisection values of each patient with those of the control group. In the E+ condition, we found a significant difference in one out of four patients (E+ 3: Z CC=2.8; p=0.013); in the E condition, we found a significant difference in two out of four patients (E+ 3: Z CC=9.4; p<0.0001 and E+ 4: Z CC=3.2; p=0.004). This greater variability in the bisection task in patients than in controls, suggests that an altered body metric re-presentation, also present in the baseline (pre-training) condition, can be associated to the body ownership disorders observed in this kind of patients.
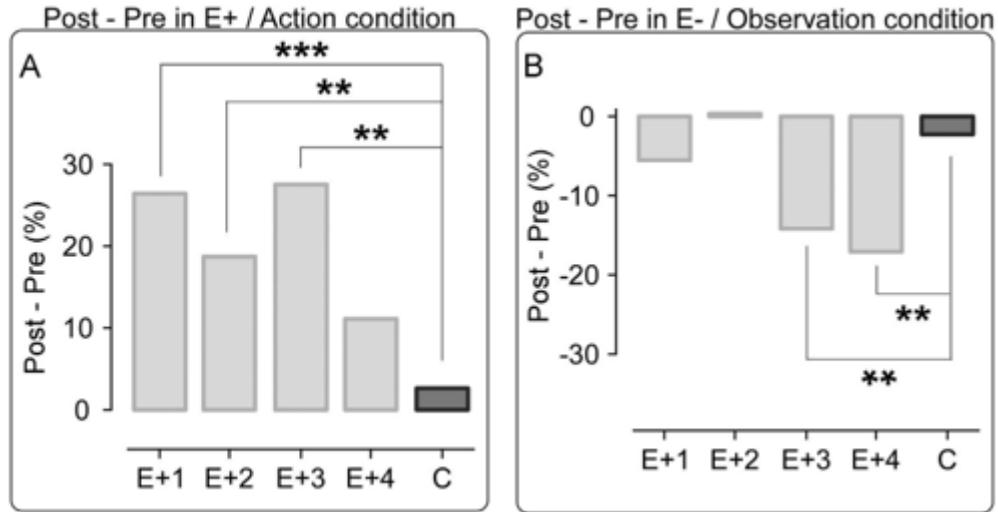
Fig. 7. Comparison between patients (Experiment 2) and healthy subjects (Experiment 1). (A) Bar plot showing the effect of tool use training (Post Pre) on Arm's length estimation in single patients and in control subjects (E+ and Action condition, respectively). A general overestimation effect is evident. Overestimation effects in single patients are compared with those in the control group. (B) Bar plot showing the effect of tool use Observation (Post Pre) on Arm's length estimation in single patients and in control subjects (E and Observation condition, respectively). A general tendency to underestimation of arm length is apparent. Under-estimation effects in single patients are compared with those in the control group. ***p<0.0001; **p<0.001; *p<0.01.

4. Discussion

In the present work we sought for evidence that the influence of tool-use training on the body spatial representation is affected by body ownership. Two experiments were carried out, one involving healthy subjects (Experiment 1), the other involving brain-damaged hemiplegic patients with pathological embodiment of an alien arm (Experiment 2). In Experiment 1, we asked whether tool-use actions with the own arm or observing an alien arm using tools can induce comparable modulation effects on the body spatial representation. In Experiment 2, the main question was whether an altered sense of ownership of body parts (embodiment of an alien arm) 1) extends to the representation of the movement of the alien arm using tools and 2) modulates the sensory map of the own arm. In Experiment 1, healthy subjects actually performed a tool-use training (Action condition), or observed the examiner's arm performing the training (Observation condition). In the Action condition, an overestimation effect of their forearm length was found; namely significantly greater forearm bisection values in the post-than in the pre-training phase were apparent. On the contrary, in the Observation condition, no significant difference was found, either when subjects held a similar tool in their hand (with-tool condition) or when they did not (without-tool condition). No difference between left hand and right hand training was found. In the experiment with hemiplegic patients (Experiment 2), although the patients were explicitly required to try to perform an active task with their own plegic arm, the tool-use training was always performed by the examiner's arm (as in the Observation condition of Experiment 1), acting in two different positions, aligned (E+) or misaligned (E-) with respect to the patients' shoulder. Crucially, in the E+ condition, where the embodiment occurred (i.e. patients were convinced to perform the tool-use training with their own (paralyzed) arm), a significant over-estimation effect was found (as in the Action condition

with normal subjects): patients mislocated their forearm midpoint more proximally to the hand in the post than in the pre training phase. Conversely, in the E condition, when the pathological embodiment did not occur, they did not show any overestimation effect. The results of Experiment 1 replicate previous findings (Sposito et al., 2012; Cardinali et al., 2011), confirming that, in healthy subjects, active tool-use induces dynamic changes in the re-presentation of body metrics. In line with Sposito and coworkers' findings, no training-dependent difference between the non-dominant (left) and the dominant (right) hand training was found. However, at least one study, employing different training tasks, has found significant differences between the dominant and the non-dominant hand in the augmentation of body representation following tool use (Rademaker et al., 2014). This different result between Rademaker et al. and our study can be ascribed to the different skillfulness level needed to perform the tasks involved in the two experiments: holding a cotton ball with a chopstick with the right and left hand simultaneously in Rademaker et al. experiment (difficult task, higher skillfulness); using a garbage plier to retrieve targets with the left or the right hand in ours (easy task, lower skillfulness). Hence, given that skillfulness is higher for the dominant than the non-dominant hand, and it positively correlates with the probability of body representation modulation by tool use (Rademaker et al., 2014), it follows that in more difficult tasks (such as that of Rademaker et al.'s it is more likely that differences can be detected between the dominant and the non-dominant hand, whereas this is less likely to be the case in easier tasks (such as that used in our experiment), where similar performances can be expected between the two hands. Going back to Sposito et al. findings, differently from their results, in our experiment healthy participants showed average forearm midpoint estimation below 50% in both the pre- and the post-training conditions. This may be related to fact that the Experiment 1 sample was made of elderly individuals (57-90 years of age, mean 70.5 ± 10.6), matched for age and educational level with E+ patients tested in the

Experiment 2, whereas in Sposito's experiment healthy subjects were university students. We might speculate, to this respect, that elderly subjects tend to underuse their upper (and, possibly, lower) limbs, due to restricted movement capabilities and necessities, resulting in absolute underestimation of upper (and lower) limbs length (but relative overestimation following tool-use training). On the other hand, absence of a similar effect in the Observation condition suggests that, at least in our sample, active tool-use is necessary in order to induce dynamic changes in the body-metrics representation, whereas tool-use observation alone is not sufficient. However, some effects of tool-use observation on space representation were found in previous works. In particular, Costantini and co-workers (Costantini et al., 2011) showed that observing an alien arm performing finalized actions with a tool may extend the representation of the reaching space of the observer, but only when the latter shares the same action potentialities with the agent, i.e. when holding a tool compatible with the goal and the spatial range of the observed action. In our experiment we could not replicate this result: holding or not the same tool as the experimenter, while observing his/her arm retrieving targets with the garbage plier, did not induce spatial extension of the observer's reaching space (that is, it did not significantly influence the subject's estimation of the midpoint of his/her own forearm). A number of factors can account for the discrepancies of the results between the two experiments. Firstly, the two studies might measure a different kind of representation: a space representation in Costantini's et al. experiment, and a body representation in the present report. Even though the peripersonal space representation and the body schema are tightly linked (e.g. Cardinali et al., 2009), they can be measured in different ways. Secondly, the dependent variables used in the two studies are different response time (RT) of the observer in the case of Costantini's et al. experiment, forearm bisection value in our experiment – and, therefore, might be differentially sensitive to the phenomenon investigated. It may well be the case that RT is

a more sensitive measure of spatial remapping than forearm bisection. Thirdly, while it is possible that during the observation of finalized actions with a tool a mirror mechanism is activated (Rizzolatti et al., 2001) that is robust enough to remap the spatial representation of the observer in a RT task such as that employed in the Costantini's et al. study, it is also likely that the same mirror mechanism is not strong enough to significantly modify the sensory representation of the observer's arm in the forearm bisection task devised in our study. Indeed, appropriate visuomotor and proprioceptive feedback signals may be necessary to obtain the above mentioned remapping of the observer's arm length representation. Although very tentative, a possible explanation could be that, during the observation of finalized actions performed with a tool, the inhibitory process known to prevent the imitation of the observed actions (e.g. Stamos et al., 2010; Mukamel et al., 2010), can have some role in preventing the updating of the body schema and, in turn, the body spatial remapping. It could be hypothesized that it is more demanding for the nervous system, in terms of energetic expense, to activate the plastic processes underlying the re-modulation of the sensory map of one part of the body, than those necessary to re-map a spatial sector (e.g. far space) into another (e.g. near space). The above mentioned inhibitory mechanism could also be somehow related to the opposite underestimation trend, shown in the Observation condition at least in some subjects. It is worth noting that the Observation condition is crucial for distinguishing between remapping effects induced by motor activation or by attentional processing. Indeed, if attentional mechanisms could fully explain the effects found following tool-use (e.g., Holmes et al., 2008), similar results should be expected in Action and Observation conditions, where the subject's spatial attention is equally involved (in both conditions the subject has to pay attention to the tip of the garbage plier, grasping targets in far space and putting them in the requested box); and this is not the case. In Experiment 2, instead, E+ patients showed an over-estimation of their own forearm length after tool-use training

performed by the alien (embodied) arm. This clearly suggests that an altered sense of body ownership of someone else's arm can extend to intentional motor processes and modulate own body spatial representation. Furthermore, comparing the results of single patients with those of the sample of healthy subjects, the overestimation effect revealed by each patient during the E+ condition was greater than that found in healthy subjects during the Active condition (the difference was significant in three out of four patients at Crawford test), suggesting that when body awareness is selectively impaired, the body-metrics representation is more susceptible to be altered. According to previous studies (e.g. Garbarini et al., 2012; Pia et al. 2013b; Garbarini et al., 2013a; Gondola et al., 2014), hemiplegic patients fully aware of their paralysis, when asked to try to perform motor acts with their paralyzed hand/arm, do not produce any effective motor programming. However, when a pathological embodiment occurs, as in the E+ condition of our experiment, the delusion of ownership affects both the motor awareness and the sense of agency (patients, although not anosognosic before the task – see Table 1 – are firmly convinced to perform the tool-use training with their own plegic arm). This, in turn, might automatically trigger intentional motor processes for the own plegic arm, which generate the updating of the body schema and lead to the remapping of one's own forearm length (similarly to healthy subjects actually performing the tool use training in the Active condition). It is important to note that the delusion of ownership, as it is also evident in the rubber hand illusion (Pavani et al., 2000; Farnè et al., 2000; Costantini and Haggard, 2007), is observed only when the alien hand is located, in egocentric coordinates, in a plausible position, compatible with the observer body schema. If this condition is not fulfilled, as in the E- condition of our experiment where the alien hand is misaligned with respect to the patients' shoulder, the embodiment does not occur. In this case, patients immediately ascribe the movements to the examiner's arm and, although required to try to perform the task as in the E+ condition, de facto

observed the examiner performing the task, and do not show any significant remapping of their forearm length, similarly to healthy subjects during Observation conditions. According to Cardinali et al. (2009) "the body schema does not accept any incoherence. This mean that when a conflict occurs between two inputs" as, in our case, two left/right hands on the table, "the brain solves it in the direction of one of them" (p. 5). We can speculate that, in this kind of patients, when the body representation is altered, the more coherent position for the arm/hand (i.e. when the arm is perfectly aligned with the shoulder and close to the body) can orient the patients' sense of body ownership. Finally, in the observation condition, it must be acknowledged the presence of a non-significant tendency towards underestimation of the one's own arm length in the majority of control subjects and in two out of four patients. This tendency was significantly greater in the two patients than in healthy subjects. These results were unexpected and we do not have yet a convincing explanation for it. Nevertheless, they might be worth of further investigation in their own right on a larger sample of patients. The possibility exists that they are related to a specific inhibitory mechanism activated during the observation of someone else's finalized actions preventing action execution when contextual conditions (passive observation of someone else's movement or imaging one's own movement) are inadequate to trigger the anticipatory neurocognitive plastic processes (e.g. space and body metrics remapping) subserving a future action. From an anatomical point of view, previous studies (Garbarini et al., 2013a, 2014; Pia et al., 2013a) described left-side embodiment following right-brain damage. Here, for the first time, a right-side embodiment following left-brain damage was described in patient E+1 (see Fig. 2). This suggests that, although it seems to be more frequently associated to right-brain lesions, this phenomenon is not related to a specific function of the right hemi-sphere. Although this datum needs further investigation on a larger sample of patients, it suggests the presence of a right hemi-sphere dominance for the building

of the sense of body ownership rather than an absolute lateralization of this function in the right

hemisphere (see also Tsakiris et al., 2008). According to previous studies (Garbarini et al., 2013a,

2014; Pia et al., 2013a), pathological embodiment is related to damage to subcortical motor

structures (basal ganglia: globus pallidus, putamen) and periventricular white matter. Lesions

locations of patients tested here is compatible with this pattern (see Fig. 2), that is also consistent

with the one identified for being responsible for somatoparaphrenia (Gandola et al., 2012), thus

suggesting a common locus for the two complementary body awareness disorders. Following

Gandola et. al. interpretation, we can hypothesize that a damage to the white matter tract linking

subcortical structures with cortical sensory-motor and associative areas may prevent the integration

of afferent information arising from the affected body part (bottom-up processes) with higher-order

and pre-existing body re-presentations (top-down processes) leading to a deficit in the construction

of a coherent body representation (Tsakiris et al., 2006, 2007, 2008). We may speculate that when

the representation of the contralesional hand is partially impaired or made fragile by the brain

damage, as in E+ patients, the brain solves the incoherence of the "mutilated" body representation

by automatically incorporating an alien hand so to regain consistency and functionality. In

conclusion, these findings demonstrate that, in presence of a delusion of ownership of a body part,

the alien body part can be so deeply incorporated into one's own body schema to extend to action

execution and to induce measurable dynamic changes in the body-metrics representation

comparable to those observed during really executed movements. This phenomenon is still far from

being fully understood at the level of its neurocognitive mechanisms and a number of important

questions still need to be answered. For example, the role of motor intentionality in the emergence

of the sense of body ownership needs to be more deeply investigated. Does embodiment of an alien

arm equally develop in absence of intention to move the own paralyzed arm, e.g. if the patient is

asked to passively observe someone else's arm movement? Or, else, do patients with embodiment show similar remapping of one's own hemiplegic arm's length representation when asked only to imagine to reach for far objects with a tool? Despite being only on the verge of a full understanding of the embodiment phenomenon, the so far collected experimental results, if further confirmed on a larger sample of patients, might have important fallbacks in the domain of neuropsychological rehabilitation. For example, it could be the case that hemiplegic patients with embodiment of an alien arm might benefit more from an observational motor training (i.e. a motor training actually performed by an alien arm) than a passive motor training, where embodiment does not occur.

4.1. Limitations of the study

We acknowledge a number of limitations of the present study: 1) the design adopted in both elderly controls (Experiment 1) and brain-damaged patients (Experiment 2) was not the ideal one. In both experiments, in order to avoid sequence effects, patients and controls were tested in two different experimental sessions (at one week distance) and we preferred not to add further experimental sessions, although this choice compromised the optimal full within-subject design, with three experimental sessions in Experiment 1 (Action; Observation with-tool; Observation without-tool) and with four experimental sessions in Experiment 2 (E+ condition with- and without-tool; E-condition with- and with-out-tool); 2) different instructions were –necessarily- given to control subjects in the Observation conditions (they were requested to stay still and to observe the examiner's arm performing the task), and to patients in the E+ and E- conditions (they were required to perform an "active" task, being asked to "try" to use the garbage plier with their plegic hand), thus rendering the two experiments not fully comparable. On the one hand, in Experiment 1, the

Observation conditions (with- and without-tool) were introduced in order to exclude the possibility that a visual feedback alone (vision of the alien arm using the tool) can be able to alter the body metric representation. If so, all the effects found in patients could be ascribed to the visual feedback and not to the pathological embodiment. On the other hand, in Experiment 2, in order to compare the results of the patients' E+ and E- conditions with those found in healthy controls actually performing the tool-use training, it was crucial to ask the patients to perform an active task.

Chapter 3

Decreased motor cortex excitability mirrors own hand disembodiment during the rubber hand

illusion

3.1 Introduction

The sense of body ownership (i.e. the belief that a specific body part belongs to one's own body) (Gallagher, 2000) is a fundamental aspect of self-consciousness. Apparently, in normal conditions, the feeling of body ownership does not need any particular explanation; it is immediate and even obvious. However, both pathological cases after brain damage (somatoparaphrenia [Romano et al., 2014] and pathological embodiment [Pia et al., 2016; Fossataro et al., 2016; Garbarini et al., 2013, 2014, 2015; Pia et al., 2013; Garbarini and Pia, 2013]) and experimental manipulations in healthy subjects (e.g. the rubber hand illusion – RHI [Botvinick and Cohen, 1998]) suggest that body ownership, as we normally experience it, is the product of many different and complex operations. It has been suggested that the feeling that our body belongs to us presumably depends on multisensory integration processes arising within a fronto-parietal network, where sensory inputs coming from different modalities are realigned in a unique reference frame (Blanke et al., 2015). Within this network, the ventral premotor cortex seems to play a crucial role, thus establishing, both in monkeys (Graziano, 1999) and in humans (Makin et al., 2008; Ehrsson et al., 2004), an anatomical link between the sense of body ownership and the motor system. Furthermore, it has been pro-posed that voluntary motor activity of body parts contributes critically to the subjective experience of body ownership (Tsakiris et al., 2010). Within this context, we asked whether the subjective and sometimes illusory sense of body ownership influences objective measures of the sensory-motor system. We took advantage of the RHI paradigm in order to provide a physiological counterpart of

the interaction between body awareness and motor control, investigating the relationship between body ownership alterations, such as those occurring during the RHI, and modulation of primary motor cortex excitability. During the RHI, the subject's real hand is out of view, while a realistic rubber hand (RH) is positioned in its place. When the experimenter synchronously strokes the index finger of both the real and the fake hand, most subjects, after a few seconds of viewing the fake hand's finger being touched, attribute their tactile sensation to the RH hand, which they start to perceive as their own. During the illusion, the subject's hand-centered reference frame shifts towards the RH, and so it has been proposed that, as a consequence, the real hand is subject to a sort of disembodiment (Ehrsson et al., 2004). Accordingly, a feeling of disownership of one's own hand has been reported as an important behavioral component of the RHI (Longo et al., 2008), while a decrease in the temperature of the real (disembodied) hand has been observed as a neurophysiological correlate of the RHI (Moseley et al., 2008). Moreover, it has been demonstrated that cooling the subject's hand increases the strength of the RHI, whereas warming the hand decreases it (Kammers et al., 2011). However, another study found that hand-cooling can be present in both the experimental (synchronous) and the control (asynchronous) condition, thus suggesting that it is not a reliable correlate of the subjective feeling of hand disownership in the RHI (Rohde et al., 2013). A further study proposed that somatosensory changes observed in the participants' hand while experiencing the RHI can be explained by cross-modal mismatch between the seen and felt position of the hand, and are not necessarily a signature of disownership (Folegatti et al., 2009).

In the present study, in the main behavioral experiment, we employed a classical RHI procedure to investigate the presence of the illusory experience in our subject sample. In addition, in the control behavioral experiment, the complementary presence of both embodiment of the RH and

disembodiment of the real hand was explicitly investigated. Moreover, during the main physiological experiment, we studied the excitability modulation of motor circuits to the real (stimulated) hand during RHI. While subjects received visual-tactile stimulations, either synchronous (to induce the illusion) or asynchronous (control condition), motor evoked potentials (MEPs) were elicited by a single-pulse of transcranial magnetic stimulation (TMS) over the left primary motor cortex (M1) and recorded from the right first dorsal interosseous muscle (FDI). See details in Material and methods and in Figure 1A.

We hypothesized that, in the motor domain, a disembodiment effect during the RHI might be measurable as a lower excitability of motor pathways to the real hand, i.e. a situation in which a stronger voluntary command is needed to bring enough motor neurons to threshold and thus to elicit movement. Thus, a decrease of FDI MEP amplitude compared to the baseline, specific to the real (disembodied) hand, was expected in the synchronous condition (where the subjects experienced the RHI) and not in the asynchronous (control) condition. Furthermore, according to behavioral studies reporting an increased illusory experience over time (Lewis and Lloyd, 2010; Valenzuela Moguillansky et al., 2013), this inhibitory motor response was expected to increase during exposure to the illusion. Finally, we expected the MEP amplitude decrease to be specific for the stimulated (right) hand, i.e. no amplitude modulation in the non-stimulated (left) hand (see Figure 1B; control physiological experiment).

3.2 Material and methods

3.2.1 Participants

Twenty-six (ten male) volunteers took part in the behavioral main experiment (mean age ± SD=24 ± 5 years) (the sample size estimation was performed according to an a priori power analysis, see details in Supplementary file 1). Additionally, a different sample of 26 subjects (ten male) (mean age ± SD=24 ± 4 years) were recruited for the behavioral control experiment. Subjects participated in the physiological experiments only if, in the embodiment questionnaire, they gave a rating higher than zero in the synchronous condition. According to this criterion, 24 out of 26 subjects participated in the physiological main experiment; 20 out of 26 subjects participated in the physiological control experiment.

All participants were right-handed, as assessed with the Edinburgh Handedness Inventory, and were screened to exclude a family history of psychiatric, neurological or medical disease. The experimental protocol was approved by the Ethics Committee of the University of Milano and written informed consent was obtained from each subject in compliance with the rules of the 1964 Declaration of Helsinki.

3.2.2 RHI experimental procedure

In both main (Figure 1A) and control (Figure 1B) experiments, the RHI was evoked by the synchronous stroking of the rubber hand and of the participant's own hidden hand (the location of stroking on the two hands was carefully matched) using the traditional visual-tactile stimulation (Botvinick and Cohen, 1998). Asynchronous stroking of a participant own hand and the rubber hand was

utilized as a control condition, in which strokes were delivered spatially and temporally out of phase between the two hands. Participants sat with their forearms resting on a table, with their right hand inserted, palm down, in one of two identical compartments of a wooden box (59 cm 33 cm 15 cm); the rubber hand was placed in the left compartment, in egocentric position and aligned with the participant's shoulder. The upper lid of the box could be lifted or lowered to either reveal or occlude the participant's view of the rubber hand in the left compartment, while his/her right hand was always out of view. The participant was able to see only the rubber hand being stroked by the experimenter's right hand, while the subject's right hand and the experimenter's left hand were always out of subject's view. The distance between the index finger of the rubber hand and the participant's own right index finger was 20 cm. A cloth was placed so as to hide both the participant's shoulder and the proximal end of the rubber hand. The behavioral RHI effect was measured in two ways: (1) by asking participants to localize the position of their unseen hand along the horizontal plan in front of them, and thus obtaining a measure of the proprioceptive drift towards the rubber hand, (2) with a questionnaire investigating their feeling of ownership of the rubber hand as a consequence of the experimental manipulation. Moreover, in the control experiment, we also measured the disembodiment experience of the stimulated hand with a questionnaire investigating the feeling of loss of own hand (Longo et al., 2008). The physiological effect was measured by recording motor-evoked potentials (MEPs), utilized to evaluate the excitability modulation of cortical and spinal motor neurons during the RHI. In the main experiment, MEPs were recorded from the real stimulated (right) hand, while in the control experiment, MEPs were recorded from the contra-lateral non-stimulated (left) hand.
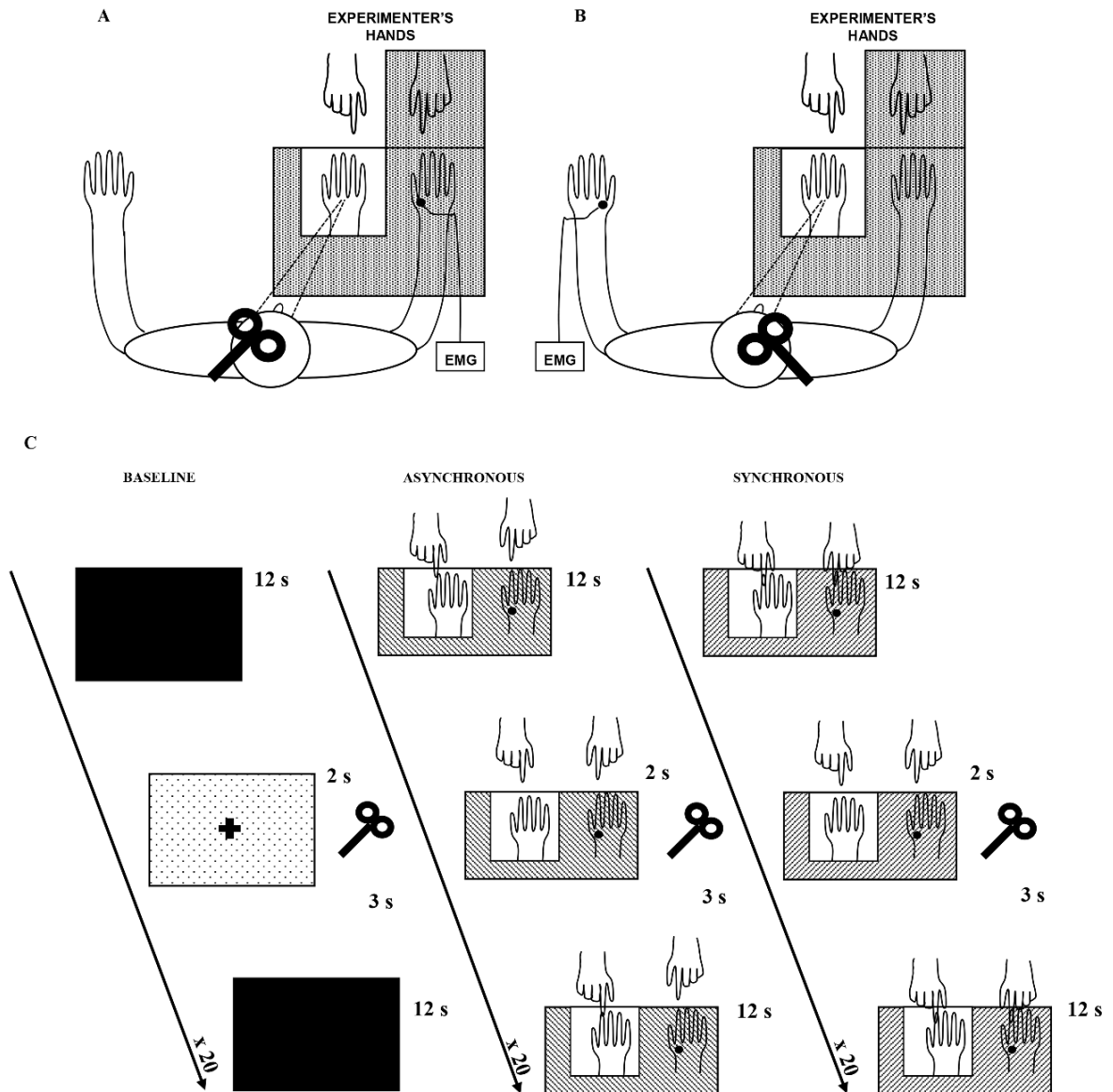
FIG 1. Experimental setup. The white square indicates the opening in the experimental wooden box through which the rubber hand is visible to the subject. Subjects could see only the rubber hand being stroked by the experimenter's right hand. In A, main experiment, MEPs were acquired from the stimulated (right) hand's FDI muscle; in B, control experiment, MEPs were acquired from non-stimulated (left) hand's FDI muscle. In C, timeline of the study and experimental conditions are plotted.

3.2.3 TMS and EMG recordings

Behavioral and physiological experiments were done in separate sessions: recording of MEPs in the three experimental conditions required about 40 min, and inserting the hand-ownership evaluation questions would have prolonged the experiment beyond a reasonable and feasible time, increasing the probability that subjects move their head with respect to the coil or lose their concentration on the task. In the main experiment, MEPs were elicited by single-pulse transcranial magnetic stimulation (TMS) of the hand area in the left M1 and recorded by self-adhesive bipolar surface electrodes that were placed over the belly of the right first dorsal interosseous muscle (FDI). Electromyography (EMG) signals were amplified, filtered (10 Hz to 1 kHz), digitally converted (sampling rate 5 kHz) and stored in a computer for offline analysis. The head of each subject was restrained by a comfortable pillow wrapping around the neck and supported by a fixed head rest. A mechanical arm held a figure-of-eight-shaped coil connected to a magnetic stimulator (Magstim 200; Magstim Co. Ltd, Whit-land, UK; maximal power 2.2 T). The coil was positioned and fixed on the left primary motor cortex with the handle pointing backwards at 45% from the midline so as to activate the selected muscle, and the stimulator output was set at about 110% of each subject's motor threshold (defined as the intensity giving three MEP responses out of six stimuli) (Rossini et al., 1994; Borroni et al., 2008). The absence of voluntary contraction before each TMS pulse was verified by continuous monitoring of the EMG signal. We replicated the same procedure in the control experiment, but in this case, MEPs were elicited by single-pulse TMS of the hand area in the right M1 and recorded with self-adhesive bipolar surface electrodes over the left FDI belly.

3.2.4 Experimental events sequence

3.2.4.1 Baseline condition

At the very beginning of each experiment, after they gave their informed consent, subjects were asked to watch a cross on a pc screen while sitting in a comfortable chair. In the meantime, 20 MEPs were recorded (without visual-tactile stimulation) and taken as a measure of motor-cortex excitability in a neutral condition.

3.2.4.2 Behavioral measurements

In both main and control experiments, participants were asked to judge the perceived location of their unseen right index finger by verbally indicating a number on a ruler presented on top of the box in front of them. This was repeated for 10 trials, and in each trial the ruler was shifted horizontally so as to avoid the subjects' basing their answers on a fixed reference point, rather than on their actual proprioceptive judgment. The difference between the indicated location of the participant's right index finger before and after the visual-tactile stimulation was taken as a measure of perceptual relocation. In order to evaluate the subjective experience of the RHI, an ownership questionnaire (emb-q-rating) consisting of three statements was administered; participants were asked to evaluate the vivid-ness of their experience of ownership of the rubber hand using a 7 points Likert scale (−3=strong disagreement; +3=strong agreement; 0=neither agreement nor disagreement), with the following three items: "It seemed as if I were feeling the touch in the location where I saw the rubber hand touched", "It seemed as though the touch I felt was caused by the touch over the rubber hand", "I felt as if the rubber hand were my hand". The statements were based on the traditional RHI study

(Botvinick and Cohen, 1998). This behavioral part was performed both to replicate results found in previous studies (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Tsakiris et al., 2010; Longo et al., 2008; Moseley et al., 2008; Kammers et al., 2011; Rohde et al., 2013; Folegatti et al., 2009; Lewis and Lloyd, 2010; Tsakiris and Haggard, 2005) on the behavioral RH effect and in order to include in the study only those subjects who experienced the illusion (with ratings higher than zero in the synchronous condition). Note that, according to this criterion, two sub-jects in the main experiment were not admitted to the physiological experiment. Moreover, in the control experiment, in order to verify whether the feeling of ownership of the RH is coherently accompanied by a feeling of disownership of the stimulated hand, a disownership questionnaire (disemb-q-rating) consisting of three statements was also administered. Participants were asked to evaluate the strength of their disembodiment experience over the stimulated hand using a 7-point Likert scale (−3=strong disagreement; +3=strong agreement; 0=neither agreement nor disagreement), with the following three items: "It seemed like I was unable to move my hand", "It seemed like I couldn't really tell where my hand was", "I seemed like my hand had disappeared". The statements were selected from a study proposing a psychometric approach to body ownership (Longo et al., 2008).

3.2.4.3 Physiological measurements

For both main and control experiments, at the end of the behavioral procedure, 20 MEPs were recorded during both synchronous and asynchronous conditions. The order of the experimental blocks (synchronous-asynchronous; asynchronous-synchronous) was counterbalanced between sub-jects. Participants received an experimental block of 20 visual-tactile stimulations, either synchronous or asynchronous, depending on the random order of the sequence. Each visual-tactile

stimulation cycle lasted 12 s. Two seconds after the end of each cycle, a single-pulse TMS was triggered to induce a MEP, using a custom-made synchronizing program in LabView10. After an inter-trial interval of 3 s, the next stimulation cycle started. Therefore, for each subject, 60 MEPs were recorded: 20 during the baseline conditions (at the beginning of the whole procedure) and 40 during the visual-tactile stimulation (20 during the synchronous block; 20 during the asynchronous). Participants were exposed to both experimental blocks (synchronous/asynchronous) in the same experimental session, with a resting break between the blocks (lasting about 5 min). The return of cortical excitability to baseline level was always ascertained before starting each block of visuo-tactile stimulation. The whole experimental procedure, including behavioral and physiological experiment, lasted about 40 min.

3.2.5 Behavioral analysis

In both main and control experiments, the mean value of the three ownership statements used in the subjective rating questionnaire, in the synchronous and asynchronous conditions, was obtained and used as a dependent variable (emb-q-rating); in the control group, we also obtained and used as a dependent variable the mean value of the three disownership statements, in the synchronous and asynchronous conditions (emb-q-rating and disemb-q-rating). For the proprioceptive drift, the difference between the indicated location of the participant's right index finger before and after the visual-tactile stimulation (in both synchronous and asynchronous conditions) was taken as a measure of perceptual relocation, which was averaged and used as a dependent variable. All data were assessed for normal distribution using the Shapiro-Wilk test ($p > 0.05$). In the main experiment, for the emb-q-rating in both synchronous and asynchronous conditions, the residuals were not

normally distributed (p=0.00146 and p=0.0092), so the Wilcoxon signed-rank test was used for pairwise comparisons. In the control experiment, in both synchronous and asynchronous conditions for the emb-q-rating (p=0.08448 and p=0.60427) and the disemb-q-rating (p=0.88009 and p=0.34168), the residuals were normally distributed, so comparisons between synchronous and asynchronous stimulations were computed by means of a paired T-test (two tailed). In both experiments, residuals for the proprioceptive drift were normally distributed (main: p=0.91975 and p=0.71247; control: p=0.90201 and p=0.37482), so comparisons between synchronous and asynchronous stimulation were computed by means of a paired T-test (two tailed). For each test performed, we reported mean, standard deviation, p (significance) value and Cohen's d value (calculated as within-subjects effect sizes using G Power matched pairs statistical tests). All subjects' behavioural data are available in an additional source data file (see Figure 2—source data 1 and 2).

3.2.6 Physiological measures and analysis

MEP amplitude of the FDI muscle was measured as the peak-to-peak distance (in MV), and MEPs of amplitude lower than 50 MV were discarded from analysis (Rossini et al., 1994; Borroni et al., 2008). For each subject, 20 measurements of MEP baseline values were acquired at the very beginning of the experiment in order to provide a reference value that could be used a) to verify that, during the on-line data acquisition, the cortical excitability was unchanged in the second experimental block of visual-tactile stimulation compared to the first one and b) to compare, during data analysis, the obtained MEP values in the experimental blocks (in order to discriminate between facilitation or inhibition effects). Normal distribution of the residuals was checked using the Shapiro-Wilk test (p>0.05), and the appropriate non-parametric tests were applied when one or more of the

corresponding data sets failed to meet the criteria for normal distribution. In both experiments, for each subject, we used MEPs recorded in each experimental condition (baseline, asynchronous and synchronous trials, a total of 60 trials), to obtain a grand-mean and a grand-standard-deviation. Then, each single trial was transformed in z-scores, according to the following formula: (x – grand-mean)/ (grand-standard-deviation), where x indicates a single trial value. The obtained values were averaged for each subject and entered into two separate (for the main and control experiments) three-level (baseline, asynchronous, synchronous) one-way ANOVAs. In this analysis, for the main experiment, the distribution of residuals in the synchronous condition was not normal (respectively: p=0.70962, p=0.08347, p=0.00604). Thus, we performed Friedman non-parametric ANOVA in order to detect significant differences across the three conditions (baseline, asynchronous, synchronous); therefore, Wilcoxon signed-rank tests were used for pairwise comparisons. Finally, for each pairwise comparison (N = 3), Bonferroni correction was applied (a value/n of comparisons: 0.05/3 = 0.017). In the control experiment, residuals of the three conditions were normally distributed (respectively: p=0.60988, p=0.44773, p=0.66546) and the ANOVA normality assumption was satisfied. Further-more, we investigated the time course of MEP change in the synchronous condition of both experiments in order to describe, for each subject, a MEP amplitude time-profile during the illusion. MEP z-scores for all participants were divided into four blocks of five MEPs each. The obtained values were averaged starting from 0 to 5 (TIME 1), from 6 to 10 (TIME 2), from 11 to 15 (TIME 3) and from 16 to 20 (TIME 4), and entered in a four level one-way ANOVA (TIME: one, two, three, four). Residuals for the main experiment were not normally distributed, so Wilcoxon signed-rank tests were used for within comparisons of the four-level time variable; for each pairwise comparison (N = 4), Bonferroni correction was applied (a value / n of comparisons: 0.05/4 = 0.0125). Finally, in order to compare MEP modulation in the two experiments, we avoided classical ANOVA because residuals in the main

experiment were not normally distributed. So, we calculated a delta on raw MEP amplitude between synchronous minus asynchronous for all subjects in each experiment; then the obtained values were analyzed with Mann-Whitney U-test. For each statistical test, we reported mean, standard deviation, p value and Cohen's d (calculated as within-subjects effect sizes using G Power matched pairs statistical tests). All subjects' physiological data are available in additional source data file (see Figure 3—source data 1 and 2).

3.2.7 Correlation analysis

In the main experiment, linear regressions were performed between emb-q rating and proprioceptive drift in both synchronous and asynchronous conditions and in the delta synchronous minus asynchronous. In these correlations, the distribution of residuals, checked with Shapiro-Wilk test, was not normal, so we adopted the Spearman rank-order correlation. In the control experiments, linear correlations were performed between emb-q-rating and disemb-q-rating in both synchronous and asynchronous conditions and in the delta synchronous minus asynchronous; moreover, linear regressions between proprioceptive drift and emb-q-rating/disemb-q-rating in both synchronous and asynchronous conditions and in the delta synchronous minus asynchronous were performed. In these correlations, residuals, when checked with the Shapiro-Wilk test, were normally distributed. We acknowledge that the present experimental design was not ideally suited to investigate correlations, due to the fact that behavioral and physiological data were acquired in two separate sessions. Indeed, we could not obtain the behavioral responses during the registration of each MEP recording (due to time constraints during MEP acquisition) and, therefore, we could not have a point-by-point matching between those data. Furthermore, only responder subjects were

admitted to the physiological experiment, i.e. we use only subjects who gave ratings higher than zero in the synchronous condition in the embodiment questionnaire administered during the behavioral experiment. Thus, in the present sample, which only includes responder subjects, correlations between physiological parameters and the presence/absence of the illusion cannot be investigated. However, to investigate whether responder subjects who experience a larger subjective illusion also show a larger decrease in MEP amplitude, we computed correlations, using either ratings of the questionnaire or proprioceptive drift values. In both cases, we used two different approaches: a) we normalized MEP values, ratings and drift values by using z-scores to compute independent correlations for synchronous and asynchronous conditions: significant correlations with MEPs were not found, neither for questionnaire ratings nor for proprioceptive drift; b) for MEP values, ratings and drift values, we computed a delta (synchronous minus asynchronous) value and performed correlations on these values: again, no significant correlations with MEPs were found for questionnaire ratings or for proprioceptive drift.
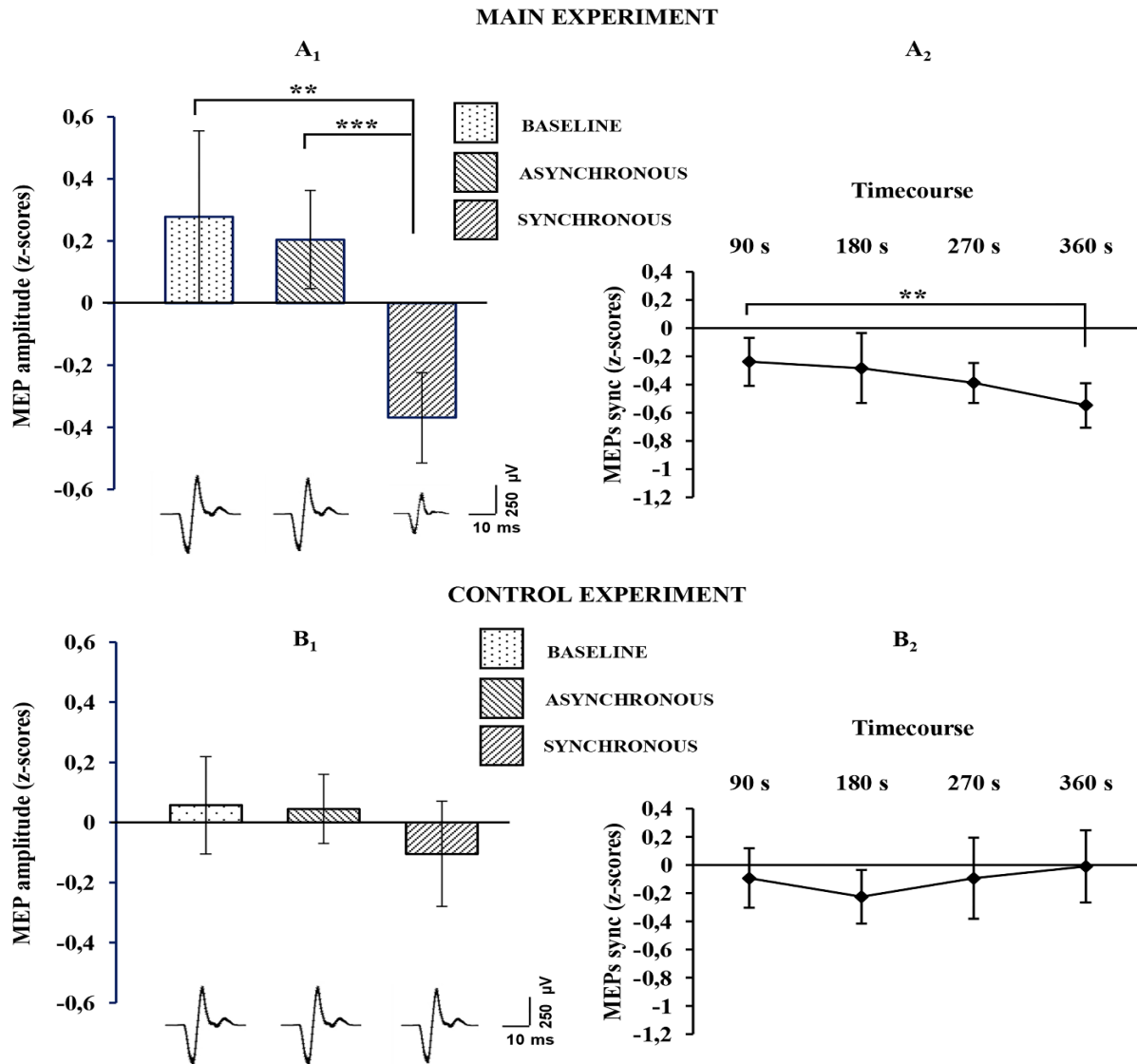
3.3 Results

The main behavioral results showed that both proprioceptive drift towards the RH and embodiment questionnaire rating (emb-q-rating) were significantly higher in the synchronous than in the asynchronous condition (drift=mean ± sd: 4.51 ± 4.2 cm vs. 2.08 ± 2.75 cm; $t_{(23)}$=2.783, p=0.0105, dz=0.58; emb-q-rating=mean ± sd: 2.4 ± 0.64 vs. 2 ± 0.9, Z=4.2857, p=0.000018, dz=3.88; Figure $2A_1$ and A_2; see also Figure 2—source data 1). No significant correlation was found between emb-q-rating and proprioceptive drift. In the control behavioral experiment, similar results were found for both proprioceptive drift and emb-q-rating (drift=mean ± sd: 2.47 ± 2.707 cm vs. 0.075 ± 2.461 cm; $t_{(19)}$=5.275, p=0.000043, dz=1.18; emb-q-rating=mean ± sd: 2 ± 0.763 vs. 0.97 ± 1.387; $t_{(19)}$=9.357, p=0.0000001, dz=-2.1; Figure $2,B_1$ and B_2; see also Figure 2—source data 2). Furthermore, the disembodiment questionnaire rating (disemb-q-rating) was significantly higher in the synchronous than in the asynchronous condition (disemb-q-rating=mean ± sd: 0.153 ± 1.427 vs. 1.15 ± 1.371; $t_{(19)}$=3.835, p=0.00116, dz==0.86; Figure $2,B_3$; see also Figure 2—source data 2). Finally, significant correlations were found between emb-q-rating and disemb-q-rating in both synchronous and asynchronous conditions and in the delta synchronous minus asynchronous (respectively: r-=-0.4911, p=0.0279; r-=-0.7128, p=0.0004; r-=-0.5537, p=0.0113; Figure $2,C_1,C_2,C_3$). No significant correlation was found between proprioceptive drift and either emb-q-rating or disemb-q-rating.

For the physiological data, the Friedman non-parametric ANOVA showed a significant effect of condition (χ^2[2, n=24] =9,000,000; p=0.01111), suggesting a difference between baseline, synchronous and asynchronous conditions, when MEPs were recorded from the stimulated (right) hand. Wilcoxon matched pairs tests, after Bonferroni correction, revealed a significant MEP decrease in the synchronous condition with respect to both the asynchronous (mean ± sd: 0.367 ± 0.362 vs.

0.205 ± 0.395; Z=3.3143, p=0.000919; dz=0.85) and the baseline (mean ± sd: 0.367 ± 0.362 vs. 0.277 ± 0.691; Z=3 .1428, p=0.001673; dz=0.74) conditions (Figure 3A$_1$; see also Figure 3—source data 1). No significant difference was found between asynchronous and baseline conditions (0.205 ± 0.395 vs. 0.277 ± 0.691; Z=0.1714, p=0.863887; dz=0.08). Examples of MEPs recorded from the FDI muscle of a representative subject are shown in Figure 3. Interestingly, the MEP time-course analysis showed that the inhibitory motor response increases over time, with lower values measured at each time-point. Note that Wilcoxon matched pairs tests, after Bonferroni correction, showed a significant difference between TIME 1 (first five trials) and TIME 4 (last five trials) (mean ± sd: 0.23963 ± 0.425821 vs. 0.5481 ± 0.394248; Z=2.942857; p=0.003252; dz=0.72), Figure 3A$_2$; see also Figure 3—source data 1. By contrast, in the control physiological experiment, in the three-level one-way ANOVA, no significant effect of condition was detected (F$_{(2,38)}$=0,894943; p=0.417068), suggesting that for the non-stimulated (left) hand there is no difference between the synchronous condition and either the asynchronous (mean ± sd: 0.104 ± 0.399 vs. 0.045 ± 0.262; p=0.820737; dz=0.26) or baseline (mean ± sd: 0.104 ± 0.399 vs. 0.0572 ± 0.368; p=0.711483; dz=0.22) conditions (Figure 3B$_1$; see also Figure 3—source data 2). Moreover, in the four-level one-way ANOVA adopted for analysis of MEP time-course, no significant effect of TIME was found (F$_{(3,57)}$=0.842673; p=0.476191), suggesting that in the non-stimulated (left) hand, MEP amplitude is not modulated over time (Figure 3B$_2$; see also Figure 3—source data 2). Additionally, the Mann-Whitney U-test revealed a significant difference between the delta synchronous minus asynchronous obtained in each experiment, showing a strong physiological effect of the RHI in the main compared to the control experiment (mean ± sd: 390.746 ± 591.662 vs. 49.0296 ± 238.332; Z=2.074180; p=0.038063).
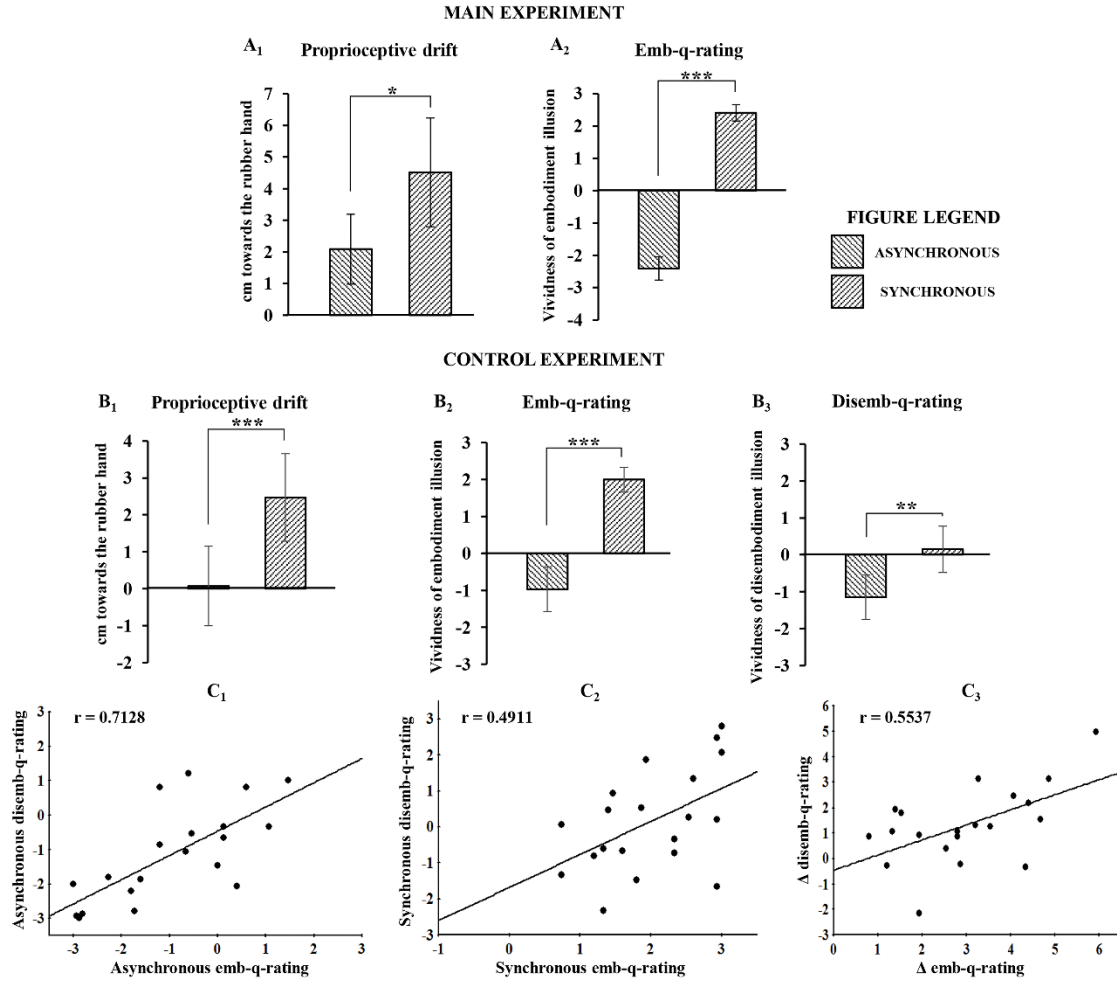
FIG 2. Behavioral results following asynchronous and synchronous condition. The average values for proprioceptive drift and emb-q-rating are plotted in A_1 and A_2, respectively, for the main experiment, and in B_1 and B_2, respectively, for the control experiments. In B_3 are reported average values for disemb-q-rating. Error bars indicate 95% CI. Significant levels: *$p<0.05$; ***$p<0.0001$. Linear regressions between emb-q rating and disemb-q-rating in both synchronous and asynchronous conditions and in the delta synchronous minus asynchronous are plotted in C_1, C_2, C_3, respectively. All subjects behavioral data are available in the additional source data file (see Figure 2—source data 1 and 2).

MAIN EXPERIMENT

CONTROL EXPERIMENT

FIG 3. Physiological results for the baseline, asynchronous and synchronous conditions. Average MEP amplitude variation in the FDI muscle recorded across all subjects are plotted in A_1, for the main experiment, and in B_1 for the control experiments. Histograms represent the peak-to-peak MEP mean amplitude (normalized) ± 95% CI in the baseline, asynchronous and synchronous conditions, respectively. Significant levels: **$p < 0.005$; ***$p < 0.0001$. Average MEP amplitude profile recorded across all subjects in the synchronous condition are plotted in A_2 for the main experiment and in B_2 for the control experiment; points represent the peak-to-peak MEP mean amplitude (normalized), ± 95% CI, at four time-points after induction of the illusion (90 s, 180 s, 270 s 360 s); significance level: **$p < 0.005$. Examples of average raw MEPs recorded from two representative subjects (for the main and control experiments) in the baseline (main: 609 μVolt; control: 619 μVolt), asynchronous (main: 771 μVolt; control: 601 μVolt) and synchronous (main:150 μVolt; control:583 μVolt) conditions. All subjects' physiological data are available in an additional source data file (see Figure 3—source data 1 and 2).

3.4 Discussion

In the present study, in order to investigate the link between body-ownership and motor system, we took advantage of the well-established RHI paradigm (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Tsakiris et al., 2010; Longo et al., 2008; Moseley et al., 2008; Kammers et al., 2011; Rohde et al., 2013; Folegatti et al., 2009; Lewis and Lloyd, 2010; Valenzuela Moguillansky et al., 2013; Tsakiris and Haggard, 2005), a useful tool to manipulate the sense of body ownership in normal subjects. In the main behavioral experiment, our data show a very strong embodiment effect in the synchronous condition (with a mean rating of 2.4, on a scale of 3 to +3), while none of the subjects reported the illusory experience in the asynchronous condition (with a mean rating of 2, on a scale of 3 to +3). A complementary disembodiment effect (Longo et al., 2008) was investigated and measured in the control behavioral experiment, showing a significant correlation between the reported ownership of the fake hand and disownership of the subject's own hand. Most importantly, the physiological results provide the first evidence that, during the RHI, the motor excitability of corticospinal hand circuits for the real stimulated hand is greatly reduced. This effect is absent for the real non-stimulated hand. In addition, consistent with behavioral studies reporting an increased illusory experience over time (Lewis and Lloyd, 2010; Valenzuela Moguillansky et al., 2013), the time-course analysis revealed that motor cortex excitability decreases as time of exposure to the illusion increases. The link between body ownership and motor system activation has been investigated with different behavioral paradigms within the RHI framework. Recently, using a moving version of the RHI, it has been shown that voluntary (but not passive) movement of the real hand decreases the perceptual shift towards the rubber hand, suggesting that the subjective sense of agency strongly contributes to a coherent sense of body ownership (Tsakiris et al., 2010). On the other hand, patients

with schizophrenia, who show a specific deficit in predicting the consequences of their voluntary actions (Voss et al., 2010), as well as an altered sense of agency (Garbarini et al., 2016; Daprati et al., 1997; Maeda et al., 2012), are more susceptible to the RHI (Peled et al., 2003; Asai et al., 2011; Thakkar et al., 2011). Other studies on clinical populations with movement disorders suggest that patients with focal hand dystonia (Fiorio et al., 2011) or partial or complete paralysis because of spinal cord injury (Scandola et al., 2014; Tidoni et al., 2014) seem to have some impairment of body ownership, according to their susceptibility to the RHI paradigm. A recent study (Burin et al., 2015), investigating the RHI in movement disorder after brain-damage, shows that hemiplegic patients display a weaker/more flexible sense of body ownership for the affected (paralyzed) hand (where the strength of the RHI is increased) when compared to controls, but an enhanced/more rigid sense of body ownership for the healthy hand (where the strength of the RHI is decreased). In other words, the prolonged absence of movement makes the paralyzed limb more readily disowned, while the healthy limb seems to be more strongly owned. Furthermore, other studies (Kilteni et al., 2016; Schütz-Bosbach et al., 2006) have investigated the modulation of corticospinal excitability during different experimental manipulations related to the sense of body ownership, though none with the specific hypothesis of linking a decrease in subjective ownership with a decrease in motor excitability. Kilteni and colleagues (2016) found that healthy people can experience a pseudo-amputation illusion during a virtual reality procedure, suggesting that this experimental manipulation causes corticospinal excitability changes in muscles associated with the virtually amputated body-part. Schütz-Bosbach and colleagues (2006) studied how an action observation task can induce different changes in corticospinal excitability, depending on the level of ownership experienced with respect to the observed moving hand. Ownership was previously manipulated using the RHI procedure: after asynchronous stimulation, observing others' actions facilitated the motor system, whereas after

synchronous stimulation, identical observed actions, now illusorily attributed to the subject's own body, evoked smaller MEPs. In light of our findings, the absence of facilitatory effect during observation following synchronous stimulation can be interpreted as resulting from the decreased corticospinal excitability induced by the illusion. Taken together, these results suggest that body ownership and the motor system are mutually interactive and both contribute to the dynamic construction of bodily self-awareness in healthy and pathological brains. In the present study, we found that the excitability of motor pathways in response to stimulation of the real (disembodied) hand is significantly decreased (i.e., MEP amplitude was significantly reduced) when subjects experience the artificial hand as their own. This suggests that an experimental manipulation of the sense of body ownership is accompanied by a coherent modulation of the motor system. However, as the experimental design was not suited to investigate correlations (see details in Material and methods), the present data do not allow us to address the question of whether subjects who experience a larger subjective illusion also show a larger decrease in MEPs. The presence or absence of linear correlations between MEP amplitude and behavioral measures, including both embodiment of the rubber hand and disembodiment of the real hand, will be investigated in future studies, in which physiological parameters of responder and non-responder subjects can be also compared. It has been suggested that active movements integrate distinct body parts into a unitary body representation (Tsakiris et al., 2010). When this unified representation is altered, as during the visual-tactile conflict induced by the illusion, the excitability of the primary motor cortex is also altered, suggesting that the motor readiness of the real (disembodied) hand could also be reduced. We ascribe the excitability decrease in the primary motor cortex (M1) to cortical inhibitory processes tied to the central processing of hand ownership, possibly reaching M1 via inhibitory input from the premotor cortex (which is known to play a crucial role in the multisensory integration processes that

give rise to the sense of body ownership) (Ehrsson et al., 2004). The present findings, which shed new light on our understanding of the different aspects that contribute to the formation of a coherent self-awareness, suggest that bodily self-consciousness strictly depends on the possibility of movement. The bodily self is primarily and originally construed in terms of motor potentiality for actions (Gallese and Sinigaglia, 2010). If I believe that the hand is mine, then I must be ready to use it; if not, then the activity of the motor system is accordingly down-regulated.

Chapter 4

GENERAL DISCUSSION

The aim of this thesis is to shed new light on the contribution of the sensory-motor system to the experience of one's own body, combining the phenomenological conception of the bodily-self and the scientific investigation of the cognitive processes underlying it. Starting from phenomenology, the conscious experience of *being-in-the-world* rises from our body and has a dual structure: a *pre-reflective* (*lived*) sense of the body and a *reflective* (*thought*) sense of the body (Husserl, 1936; Merleau-Ponty, 1962). Recently, also cognitive neuroscientists have begun to recognize the central role of the body as the origin of our conscious experience (Csordas, 1990; Thompson and Varela, 2001; Heiner, 2008; Barsalou, 2008; Gallagher, 2005; Gallese & Lakoff, 2005; Proffitt, 2006), by focusing their experimental investigation on the processes underlying the experience of a coherent sense of body ownership. The complex experience of body ownership is conceptualized as being shaped by different sub-components: a body schema, i.e. an implicit sensory-motor representation of the body, which corresponds to the phenomenological *pre-reflective* sense to own a body; and a body image, i.e. the explicit representation of the body in terms of visual, sensory-motor and emotional features, which corresponds to the *reflective* sense to own a body. The continuous interaction between the two is constantly shaped by the *sense of embodiment*, process on which we rely in order to experience an "object" (including all our body parts) *as part of our body* (de Vignemont, 2011)*.* For instance, when we use a tool, the boundaries of our body are *extended*, objects we want interact with, previously out of our hand reaching space, are perceived as closer to us, and the tool then becomes a ''*bodily auxiliary, an extension of the bodily synthesis*'' (Merleau-

Ponty, 1962, p. 152). Merleau-Ponty said: "*The blind man's stick has ceased to be an object for him, and is no longer perceived for itself; its point has become an area of sensitivity, extending the scope and active radius of touch, and providing a parallel to sight*" (1962, p. 143). Recently, changes in our perceived *body-environment-space* occurring during tool-use (Maturana & Varela, 1987) have been described with a multidisciplinary approach: in physiology (Graziano et al., 1994; Fogassi et al., 1996; Duhamel et al., 1996; Iriki, Tanaka and Iwamura, 1996), in neuropsychology (Marshall & Robertson, 2013; Berti & Frassinetti, 2000; Neppi-Mòdona et al., 2007) and in cognitive science (Sposito et al., 2012, Cardinali et al., 2009; Costantini et al., 2011; Maravita et al, 2002). However, ''*the feeling of ownership that we have for our bodies clearly does not extend to, for example, the fork we use at dinner*" (Botvinick, 2004, p. 783). In this view, it seems that the embodiment of a tool does not include a full sense of ownership, and only modifies the motor side of the body representation (De Preester & Tsakiris, 2009). Therefore, it would be more appropriate to talk about a change in the sense of ownership when a non-corporeal embodied object fits in with a pre-existing model of the body that regulates which objects sufficiently resemble body-parts, based on postural, anatomical and visual clues (as in the case of the RHI) (Tsakiris, 2010). Body ownership is deeply interconnected with the feeling that we are in control of what we are doing with an "object"; this *sense of agency* (Gallagher, 2005; Haggard et al., 2002; Tsakiris, 2010) results in the experience of oneself as owning a body as agentive (Gallese & Sinigaglia, 2011). From a neural point of view, it has been suggested that body ownership is served by processes that integrate multisensory signals concerning our body, the space around us and the possibility to move in the environment. In turn, those processes are served by a network that comprehends high-order associative brain areas (Ehrsson et al., 2004; 2005; Blanke et al., 2015; Martel et al., 2016) in which somatosensory and motor information seem to play a crucial role in the emergence of body ownership. It appears that focusing on aspects of

object embodiment (such as tools or RH) may offer a very valuable resource to investigate high-order body representations and their plasticity (Martel et al., 2016). Within this context, in order to better describe the contribution of sensory-motor system to body ownership, this thesis focused on two experimental models: body ownership alteration following brain injuries (pathological embodiment, Chapter 2) and disruption of body ownership following multisensory illusion (rubber hand illusion, Chapter 3).

The study presented in Chapter 2, sought behavioral evidence supporting the idea that the influence of tool-use training (grasp to place via garbage plier) on the body spatial representation is affected by a distorted body ownership in brain damaged patients. The patients we described claim to own someone else's arm when the alien arm is egocentrically aligned with the patient's contralesional shoulder (E+ condition). The main question was whether an altered sense of ownership of body parts (embodiment of an alien arm) 1) extends to the representation of the movement of the alien arm using tools and 2) modulates the sensory map of the own arm. A control group of healthy subjects (Experiment 1) were asked a) to actually perform the tool-use training with their own arm (action condition) or b) to observe an alien arm (the examiner's arm) performing the tool-use training, while holding (observation with-tool condition) or not (observation without-tool condition) a similar tool. The results of Experiment 1 replicate previous findings (Sposito et al., 2012; Cardinali et al., 2009), confirming that, in healthy subjects, active tool-use induces dynamic changes in the representation of body metrics. On the other hand, we did not replicate the findings of Costantini and colleagues (2011), which showed that observing an alien arm performing finalized actions with a tool may extend the representation of the reaching space of the observer, but only when the latter shares the same action potentialities with the agent. In our experiment in healthy subjects, active tool-use is

necessary in order to induce dynamic changes in the body-metrics representation, whereas tool-use observation alone is not sufficient. In Experiment 2, patients were asked to try to perform the tool-use training with their own (paralyzed) limb, while the alien arm performed the tool-use training acting either in the E+ position, where the pathological embodiment systematically occurs, or in the E- position, where the embodiment does not occur. In the E+ condition patients showed an over-estimation of their own forearm length after tool-use training performed by the alien (embodied) arm. In the E- condition they did not show any overestimation effect. This clearly suggests that an altered sense of body ownership can extend to intentional motor processes and modulate own body spatial representation. Furthermore, comparing the results of single patients with those of normal subjects' sample, the overestimation effect revealed by each patient during the E+ condition was greater than that found in healthy subjects, suggesting that when body ownership is selectively impaired, the body-metrics representation is more susceptible to being altered (effect that could also be driven by the severity of brain circuit lesions). More interestingly, this delusion of ownership affects both the motor awareness and the sense of agency (patients, although not anosognosic before the task are firmly convinced to perform the tool-use training with their own plegic arm), which in turn, might automatically trigger intentional motor processes for the own plegic arm and generate the updating of the body schema, resulting in the remapping of one's own forearm length (similarly to healthy subjects actually performing the tool use training in the Active condition). Neuroimaging data showed that pathological embodiment is related to damage to subcortical motor structures (basal ganglia: globus pallidus, putamen) and periventricular white matter (Garbarini et al., 2013a, 2014; Pia et al., 2013a). This pattern is consistent with the one identified for being responsible for somatoparaphrenia (Gandola et al., 2012), suggesting a common locus for the two complementary body awareness disorders. In E+ patients seems that a damage to the white matter

tract linking subcortical structures with cortical sensory-motor and associative areas may prevent the integration of afferent information arising from the affected body part (bottom-up processes) with higher-order and pre-existing body representations (top-down processes), leading to a deficit in the construction of a coherent body representation (Tsakiris et al., 2006, 2007, 2008). In line with that, this condition might also be interpreted as a disconnection deficit. In E+ patients, given the subcortical and white matter lesions, hard-wired body representations could result isolated from their sensory counterpart; this deficit would entail patients to experience part of the body belonging to other individuals and may generate on it intense sensory experiences such as those experienced on their real limbs. Alternatively, we may speculate that when the representation of the contralesional hand is impaired or made fragile by the brain damage, as in E+ patients, the incoherence of the "mutilated" body representation is solved by automatically incorporating an alien hand in order to regain consistency and functionality.

In Chapter 3, in order to investigate the link between body ownership and motor system, we physiologically studied the state of sensory-motor system during the RHI, a useful tool to manipulate the sense of body ownership in healthy subjects (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Tsakiris et al., 2010; Longo et al., 2008; Moseley et al., 2008; Kammers et al., 2011; Rohde et al., 2013; Folegatti et al., 2009; Lewis and Lloyd, 2010; Valenzuela Moguillansky et al., 2013; Tsakiris & Haggard, 2005). The processes behind the *incorporation* of the RH are still under debate; according to the body-model constrains, embodiment must respect some basic anatomical restrictions, so that *only some objects under certain circumstances can be processed as if they were parts of one's body* (de Vignemont & Farnè, 2010). It follows that there can be only two hands represented, a left hand and a right hand, so, one should expect the embodiment of the rubber hand to be associated with a

disembodiment of the biological hand, as if the biological hand were replaced by the artificial one (de Vignemont & Farnè, 2010). Based on this assumption, we expected that a disembodiment effect during the RHI might be measurable as a lower excitability of motor pathways to the real hand; we hypothesized that if the RH *really* replaces the real hand, allowing subjects to experience *disownership* towards it, then this very high-order experience should also be reflected in a decreased activity of the sensory-motor system underlining the motor control of the biological (deluded) hand. In particular, we studied the excitability modulation of the primary motor cortex areas controlling the real (stimulated, right) hand (Experiment 1) and the contralateral (not stimulated, left) hand (Experiment 2_control). In Experiment 1, while subjects received visual-tactile stimulations, either synchronous (to induce the illusion) or asynchronous (control condition), motor evoked potentials (MEPs) were elicited by a single-pulse of transcranial magnetic stimulation (TMS) over the left primary motor cortex (M1) and recorded from the right first dorsal interosseous muscle (FDI) with self-adhesive bipolar surface electrodes. In Experiment 2, we replicated the same procedure, but in this case, MEPs were elicited by single-pulse TMS of the hand area in the right M1 and recorded the left FDI. In both experiments, behavioral data (questionnaire and proprioceptive drift) show a very strong embodiment effect in the synchronous condition; moreover, a disembodiment effect (Longo et al., 2008) was investigated and measured in the control experiment, showing a significant correlation between the reported ownership of the fake hand and dis-ownership of the subject's own hand. These behavioral data are in favor of the *replacement* hypothesis, so that when subjects report feeling of ownership over the RH, they contemporary report feeling of dis-ownership towards their real hand. Most importantly, the physiological results provide the first evidence that, during the RHI, the motor excitability of corticospinal hand circuits for the real stimulated hand is greatly reduced (Experiment 1). This effect is absent for the real non-stimulated hand (Experiment 2). In addition,

consistent with behavioral studies reporting an increased illusory experience over time (Lewis and Lloyd, 2010; Valenzuela Moguillansky et al., 2013), the time-course analysis revealed that motor cortex excitability decreases as time of exposure to the illusion increases. These results clearly show that an experimental manipulation of the sense of body ownership is accompanied by a coherent modulation of the motor system. It has been suggested that the possibility to move constantly shape the perception of our bodily experience (Gallese & Sinigaglia, 2011) and that active movements integrate distinct body parts into a unitary body representation (Tsakiris et al., 2010). When this unified representation is altered, as during the visual-tactile conflict induced by the illusion, the excitability of the primary motor cortex is also altered, suggesting that the motor readiness of the real (disembodied) hand could also be reduced. We ascribe the excitability decrease in the primary motor cortex (M1) to cortical inhibitory processes tied to the central processing of hand ownership, possibly reaching M1 via inhibitory input from the premotor cortex (which is known to play a crucial role in the multisensory integration processes that give rise to the sense of body ownership) (Ehrsson et al., 2004; 2005; Blanke et al., 2015). However, a limitation of the study is that our measure does not tell the whole story about "that's my hand" recognition pattern process, and we can neither be sure that only the premotor cortex produces active inhibition on M1 (which in this vision could results a readout-only) nor exclude the possibility that M1 does really participate to the building-up of *hand-myness.* Further investigations, both structurally and functionally, and more compelling evidences are needed to better clarify the role of sensory-motor system in hand/body ownership. This work had the goal to do so and represents a major advance in our understanding of the sense of body ownership by demonstrating that the state of the sensory-motor system is intimately tied to a limb's current state of embodiment (Miller & Farnè, 2016).

In conclusion, the results presented here shed new light on our understanding of the different aspects that contribute to the formation of a coherent self-awareness. In both Chapter 2 and 3 we showed that body ownership and the motor system are mutually interactive and that both contribute to the dynamic construction of bodily self-awareness in pathological and healthy brains. Patients with primary sensory-motor impairment and right parietal lesion do not recognize their limbs as their own and perceive them as belonging to others (somatoparaphrenia) or, under certain circumstances, claim to own someone else' limb (pathological embodiment, Chapter 2). On the other hand, when in healthy subjects an experimental body ownership alteration causes feeling of dis-ownership towards one's own hand (RHI, Chapter 3), the excitability of the sensory-motor circuit for that hand is decreased. According to the body-model hypothesis, in order to experience ownership over a body part, whatever the nature of the embodiment process, pathological (Chapter 2) or physiological (Chapter 3), several constrains have to be respected: body-specificity (viewed object has to resemble a body-part, and not a neutral object), anatomical restrictions (the body-part has to be in a posture that is anatomically plausible and congruent with the posture of the subject's own body-part), and body-part identity (same handedness as the subject's stimulated body part) (Tsakiris et al., 2007; Tsakiris, 2010). By contrast, it has recently been reported that people can have the experience that an artificial hand is a supernumerary limb belonging to their own body (Gusterman et al., 2011). This perceptual illusion arises when a rubber hand is placed beside the participant's real hand in full view and both hands are brushed on corresponding sites in a synchronous manner. These findings challenge the traditional view of the gross morphology of the human body as a fundamental constraint for own-body perception, and instead suggest a highly flexible model of the body representation, which can be reshaped to include an extra limb.

These evidences show that the sense of embodiment is phenomenologically complex and its relationship with body ownership is far from being fully understood. It follows that the body-model hypothesis needs to sharpen its basic assumption of what embodiment is, how it relates to body ownership and which are the conditions that designate an object as embodied (de Vignemont, 2011); in fact, not always the embodiment of an objects is reflected in a perceived change in the feeling of ownership, as in the case of embodiment of tools (Botwinick, 2004), possibly because there is no visual correspondence between the tool and a pre-existing high-order model of our body (De Preester & Tsakiris, 2009). Furthermore, under certain circumstances, such as the RHI (as well as in disorders after brain injuries), humans can experience somatic sensations that seem to violate the human body plan.

A good solution to this theoretical problem is (reasonably) assuming that embodiment is a necessary condition for body ownership, i.e. "*I cannot feel that an object is mine without the same object being embodied*" (de Vignemont, 2011). Moreover, embodiment should be conceived in a double appearance: perceptual and motor. The first one corresponds to the representation of the embodied object into the subject' body image (as in the case of RHI), while the second indicates the representation of the embodied object into the subject' body schema (as in the case of tools) (de Vignemont & Farnè, 2010). The authors continue arguing that:

"*perceptual embodiment and motor embodiment may follow different rules, based on the functional roles of the body representations within which external objects are integrated. Arguably, what is required for action is not the same as what is required for perception…tools can be motorically embodied, while it is still an open question whether it can be perceptually embodied. On the other hand, multiple rubber hands can be perceptually embodied, while they cannot be motorically embodied*".

According to de Vignemont and Farnè (2010), for the biological body these two processes are always present and not dissociable; but this is not the case for tools (only motor) and RH (only perceptual) embodiment.

I agree with the view that for the moment we can only account for a motor component of the experience of tool embodiment. However, the data presented in this thesis do not completely fit with the embodiment conception of bodily-shaped objects, which could be just perceptual. We showed that there is always a motor counterpart involved in perceptual embodiment, be it pathological (Chapter 2) or experimentally (Chapter 3) induced. Our findings demonstrate that, in E+ patients, the embodiment of the alien body part is so deeply felt that it extends to action execution and it induces measurable dynamic changes in the body-metric representation (Chapter 2). Moreover, during the RHI (Chapter 3), we showed that when participants feel like the RH is part of their body, the real (deluded) hand is felt less vividly, and its motor state is also lowered, providing direct motor measure of what, until now, has *only* been conceptualized as a perceptual embodiment. Gibson's theory of perception claims that we see things in relation to their possible uses and every object perception recalls a motor interaction with it (1979)*,* so why should it not be the same for a body-shaped object *temporarily* believed to be ours?

I'd like to end this thesis by proposing a change in the theoretical conception of body ownership grounded on the sense of embodiment, which bring us back to the phenomenological conception of the bodily self from which we started.

The *lived-body* (*leib*), or the implicit representation of our body, which well fits with the notion of body schema and motor embodiment, is the *first principle* of our conscious experience, and has an intrinsic and primary sensory-motor nature (Husserl, 1936; Merleau-Ponty, 1962; Gallagher, 2005). It follows that every high-order experience originates from it. The explicit representation of our

body, the *object-body* (*korper*), which well fits with the notion of body image and perceptual embodiment, cannot be conceptualized without the sensory-motor component that allows its emergence (Varela, 1996). This philosophical insight has been confirmed in a recent study on a patient who, after a vascular tumor resection at the level of medulla oblongata, reports no somatosensory sensations from the right upper limb (a condition known as *deafferentation*). The researchers showed that a tool cannot be incorporated into the patient' body schema because the lack of somatosensory sensations, and concluded that the sense of proprioception is a necessary condition for body schema dynamic change (Cardinali et al., 2016).

In my view, the sense of embodiment is an experience emerging at different levels of complexity, rather than mainly composed by two different aspects (motor and perceptual). The first step which allows us to develop the feeling of body ownership is to be sensory-motor embodied (first level); this level reflects our *unconscious* experience to have a body, and comprehends action oriented body schemas (Maturana & Varela, 1987; Varela, 1999). In parallel with one of the most important theories of cognitive development we could also indicate this stage as *sensorimotor stage* (Piaget, 1952; 1954; 1964). During this period, children's early manifestations of intelligence appear from motor activities and sensory perception, which is the reason why Piaget indicates this stages as *sensorimotor*. According to him, intellectual growth is a process of continuous adaptation to the environment, which emerges thanks to the presence of schemas. "*A schema is the basic building block of intelligent behavior a way of organizing knowledge..a set of linked mental representations of the world, which we use both to understand and to respond to situations*" (Manichander et al., 2016, pp 46). As a child gets older, his or her schemas become more numerous and elaborate thanks to two key processes: assimilation (using an existing schema to deal with a new object or situation) and accommodation (the schema needs to be changed to deal with a new object or situation).

At the end of this period, having had enough experience of interaction with the environment, we become able to mentally represent part of our previous sensory-motor experience, and from this process the sense of perceiving ourselves as perceptually embodied appears (second level). Following Piaget, we could also indicate this stage as the initial formation of *object permanence* (Piaget, 1952; 1954; 1964), which reflects a child's understanding that objects continue to exist even though they cannot be seen or heard. Is from now on that children begin to develop symbols to represent events or objects (also themselves) in the world and, during this time, they begin to move towards understanding the world through mental operations rather than purely through actions (Piaget, 1952; 1954; 1964).

Finally, from the constant interaction and co-existence of the previous levels, the complex capacity to represent ourselves as the object of our experience emerges (third level). This last qualitative leap would correspond to the beginning of *symbolic thought* (Piaget, 1952; 1954; 1964), which will result in the conscious belief to own our body. The idea being that in order to reach the third (more complex) level, one must live, retain and integrate the experience from the previous two levels. The upper level is always a new qualitative state, in which the features of the previous levels have been integrated to allow the emergence of a more complex phase of experience (Depraz, Varela & Vermersch, 2003). *Knowledge is a continuous process of construction which does not progress at a steady rate, but rather in leaps and bounds* (Piaget, 1952; 1954; 1964). Assuming that body ownership (and consciousness in general) is the result of a complex evolutionary process could allow scientists and philosophers to better understand how human beings developed the ability to think about themselves. This also implies that we should recognize a common process between different species for the emergence of body ownership and a landmark point from which we started to be consciously different. In non-human primates it has been demonstrated that the representation of

a limb as belonging to the body can be extended by experience beyond the monkey's own bodies (Iriki et al., 1996; Graziano, 1999; Graziano et al., 2000). Moreover, it has recently been described that also in non-primate animals similar changing could be observed. A group of Japanese researchers tested the RHI paradigm in rodents, developing a new paradigm called *rubber tail illusion* (Wada et al., 2016). When the real and rubber tails were synchronously stroked, the mice responded as if their own tails were touched when the rubber tails were grasped. The same responses were not observed in the asynchronous (control) condition. These findings suggest that mice may experience ownership of their tails. But the very question is: do animals experience body ownership as humans do? Considering the three different level of complexity discussed above, we would probably claim that the experience of human beings has reached the most complex state of this evolutionary chain. So my answer would be "No, body ownership is qualitatively different between humans and other animals, especially if body ownership corresponds to the positive phenomenology of *myness* that goes beyond the mere experience of bodily properties. However, if we accept this definition, we would then have to claim that animals do not experience body ownership at all, contrary to the existing experimental evidence suggesting that mammals share a very rudimental level of body ownership experience. I suggest that this level corresponds to an implicit sensory-motor experience to own a body, and this assumption could explain why non-human primates may experience motor embodiment (tool incorporation). At the same time, we can also assume that this very low level can develop into something more complex, like perceptual embodiment, otherwise it would be difficult to explain *ownership illusion* in mice (rubber tail illusion). Supposedly only humans reached the last level, which is the capacity to put themselves as the object of their own experience, always starting from the same common ground, which is the sensory-motor system.

Anyway, it seems that we are far from reaching true answers to these fascinating questions; we need to improve our tools of investigations and be careful about easy over-interpretation. A shared definition of body ownership could help all researchers from different fields to better define new protocols capturing all its aspects, in healthy and pathological brain, as well as in animals.

In light of what has been discussed, in order to improve our knowledge of the mind, researchers must turn their investigations into a multi-disciplinary approach, which can be realized only with the continuous comparison between different doctrines operating in this field. The best candidate to respond to this appeal seems to be the Neuro-phenomenological approach, which searches for a dialogue between cognitive science and phenomenology in the attempt to establish a methodology that takes into account the nature of the co-determination between the first-perspective and the third-perspective analysis of human experience (Varela, 2000).

"Neuro-phenomenology is the name I am using here to designate a quest to marry modern cognitive science and a disciplined approach to human experience, thus placing myself in the lineage of the continental tradition of phenomenology. My claim is that the so-called hard problem...can only be addressed productively by gathering a research community armed with new pragmatic tools enabling them to develop a science of consciousness"

(Varela 1996, p 330).

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APPENDIX I

SCIENTIFIC PRODUCTION

PUBLISHED JOURNAL ARTICLES RELATIVE TO THE PRESENT THESIS:

Francesca Garbarini, Carlotta Fossataro, Anna Berti, Patrizia Gindri, Daniele Romano, Lorenzo Pia, **Francesco della Gatta**, Angelo Maravita, Marco Neppi-Modona (2015) When your arm becomes mine: Pathological embodiment of alien limbs using tools modulates own body representation. *Neuropsychologia*, 70 (2015) 402–413. http://dx.doi.org/10.1016/j.neuropsychologia.2014.11.008.

Francesco della Gatta, Francesca Garbarini, Guglielmo Puglisi, Antonella Leonetti, Annamaria Berti, Paola Borroni (2016) Decreased motor cortex excitability mirrors own hand disembodiment during the rubber hand illusion. *eLife* 2016;5:e14972. DOI: 10.7554/eLife.14972.

POSTER PRESENTATION RELATIVE TO THE PRESENT THESIS:

27-29 Nov 2014, Florence, Italy. Title: *The Effect of the Rubber Hand Illusion on Motor Cortex Excitability*.

07-10 May 2015, Rovereto, Italy. Title: *The Effect of the Rubber Hand Illusion on Motor Cortex Excitability*.

29 Sept-02 Oct 2015, Baveno, Italy. Title: *Decreased motor cortex excitability mirrors own hand disembodiment during the rubber hand illusion*.

26 May 2016, Milan, Italy. Title: *The rubber hand illusion modulates the excitability of motor cortical circuits.*

AWARD PRESENTATION RELATIVE TO THE PRESENT THESIS:

01 Oct 2015, Baveno, Italy. Best Oral Presentation at the first Fall School in Neuroscience: "The adaptive brain from development to disease".