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Body ownership gates motor control and sensory perception: behavioural and physiological evidence

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General Introduction

Humans are aware not only of the environment that surrounds them but also of themselves: their experiences, their mental states and their bodies. In other words, they are self-conscious. The origin of self-consciousness has raised fierce debate in the philosophical tradition since the dawn of time. For instance, according to more empiricist accounts, the representation of one-self might emerge from the convergence of motor and sensory experiences (Penelhum, 2000). In this view, self-consciousness has been defined as nothing more than a "heap or collection of different perceptions" (Hume, 1978; Strawson, 2011). On the other side of the spectrum, it has been argued that self-consciousness might be a higher-level representation, independent of motor and sensory perception. Along this line, self-consciousness is not sensory in nature and does not require awareness of outer things (Black, 2008; Kaukua & Kukkonen, 2007; Matthews & McKenna, 2002).

Against this background, neuropsychology has been employed as a scientific tool to investigate the reciprocal relationship between self-awareness and sensorimotor experience. More specifically, it allows to study pathological conditions in which a brain damage has selectively impaired self-consciousness sparing sensorimotor perception or, vice versa, cases in which sensorimotor perception is defective but self-consciousness remains unharmed. In other words, it helps to establish whether sensorimotor perception is a necessary (or even sufficient) condition for self-consciousness or *vice versa*, and to investigate the relationship between them (i.e., whether an alteration of sensorimotor perception automatically causes an alteration of self-consciousness or *vice versa*).

Within this field of research lies the neuropsychological literature that studies the sense of body ownership, intended as the representation of the self as the subject of experience grounded into a body, whose parts are felt as one's own, differentiated from the environment and from other bodies (Gallagher, 2000; Serino, 2019). Neuropsychology has outlined that body ownership disturbances can appear following brain damage to cortical networks encompassing frontal, parietal and occipital areas (Errante et al., 2022; Moro et al., 2021), resulting in counterintuitive behaviours such as ascribing one's own body parts (e.g., a hand) to someone else [i.e., a condition called "somatoparaphrenia"; (Romano et al., 2015; Vallar & Ronchi, 2009)]. About ten years ago, a peculiar body ownership disorder was described, characterized by the misattribution of another person's hand (i.e., the examiner's) to the own body, whenever that hand is placed in a body-congruent way (Garbarini et al., 2013, 2014, 2020). Interestingly, over the last decade, it has been shown that pathological embodiment can appear irrespectively of the presence of primary motor and sensory deficits [e.g., see (Pia et al., 2020)]. The observation of patients with pathological embodiment and spared motor and sensory functions, as well as patients with sensorimotor deficits but no impairment of the sense of body ownership has offered compelling evidence that the sense of body ownership is "something else" from the simple sum of body perceptions. Indeed, this evidence has suggested that the representation of one's self body cannot be confined to a simple collection of perceptions and that losing the ability to perceive does not necessarily imply a body ownership deficiency. Having determined that the sense of body ownership does not simply emerge from sensorimotor perception, we moved the question to the investigation of how it is related to sensory and motor experience. More precisely, we asked whether an alteration of the sense of body ownership induces alterations also in motor and sensory perception, as if the former had a top-down influence on the latter. The aim of these studies is investigating whether, when we move a body part or perceive on it, the experience is confined within the boundaries of *what physically belongs to the own body* or if it pertains to *the body parts that are believed to be one's own*. In other words, if someone's body ownership is altered so that they believe that an alien hand belongs to the own body, do they "move and perceive" from the own hand (i.e., the one which is physically attached to the own body) or do they move and perceive from the alien hand (i.e., the one which is believed to be one's own)?

In the present dissertation, I will describe some recent studies that we have conducted within my PhD project to address this issue, capitalizing either on patients affected by pathological embodiment or experimental procedures able to induce a similar phenomenon in the healthy brain.

In chapter one, recent evidence in this field of research is reviewed to give some context to the reader and introduce both the pathological model and the experimental procedures employed in the following studies. Indeed, in addition to stroke patients affected by pathological embodiment described above, we have also leveraged a well-known multisensory illusion able to alter the sense of body ownership in healthy individuals, i.e., the rubber hand illusion [RHI; (Matthew Botvinick & Cohen, 1998a)]. By receiving synchronous strokes on the own hand, which is covered from view, and a rubbery fake hand, which is in a body-congruent position and clearly visible, one can experience a transient feeling of embodiment of the fake hand, altogether with a concomitant disembodiment of the real own hand. This feeling can be measured both with explicit questionnaires (Longo et al., 2008) and implicit measures, such as the drift of the own hand's felt position towards the rubber hand [i.e., proprioceptive drift; (Tsakiris & Haggard, 2005)]. Hence, in some of the studies which are described in this thesis, instead of testing brain-damaged patients, we capitalized on this experimental procedure to measure how motor control and sensory perception are altered following the embodiment of a rubber hand.

In chapter 2, the relationship between body ownership and motor control is addressed through the description of two studies, respectively investigating this issue in the pathological human brain (i.e., in patients with pathological embodiment) and in a monkey (i.e., employing the rubber hand illusion). In the first experiment (see *Study 1.1*), we tested whether, when planning a reaching movement towards an external target, a patient with pathological embodiment starts from the position of the own hand, or from that of the alien embodied hand. In this way, we addressed if, when planning a reach, we do so having in mind the hand which is physically attached to our body, or that which is believed to be one's own. In the second experiment (see *Study 1.2*), we tested whether, when performing a self-directed movement, we aim towards the physical position of our body or to the position of the body which is believed to be our own. Crucially, in this study we also addressed whether similar mechanisms are present in non-human primates, by testing a monkey with the very same reaching task and RHI protocol.

In chapter 3, the relationship between body ownership and sensory perception is tackled, by describing three studies in which behavioural, electrophysiological and brain stimulation techniques were employed to measure visual and tactile system's modulations following the RHI. In the first study (see *Study 2.1*), we investigated how visual and tactile perception is modulated by the embodiment of a fake hand, capitalizing on a behavioural detection paradigm. In the second experiment (see *Study 2.2*), we aimed to describe the electrophysiological counterparts of these effects by measuring somatosensory- and visual-evoked potentials following the RHI. Study 2.1 and 2.2 allowed us to shed light on how the brain balances the weight attributed to visual and tactile afferences in order to give rise to the bodily illusion. Finally, in the third experiment (see *Study 2.3*), to better characterize the neural mechanisms underpinning this phenomenon, we combined transcranial magnetic stimulation with electroencephalography to investigate the connectivity modulations either during the observation of touches on an embodied rubber hand, or while feeling touches on the own disembodied hand.

In conclusion, we propose a more general model that explains how body ownership gates movement and sensory perception and, in turn, how movement and sensory perception foster the development of the sense of body ownership.

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Chapter 1

The sense of Body Ownership

A fundamental component of our self-experience is the body we live in, the mean by which we perceive and act. What makes bodily sensations so special is the experience that ‘my body’ belongs to me and is ever present in my mental life, i.e., the so-called sense of body ownership (Gallagher, 2000). The feeling that we “own” our body is such an integrated part of our cognition that it is usually taken for granted. However, the study of brain damaged patients has raised the question about how deep body ownership is rooted into the human psyche, demonstrating a neural circuitry that subserves its normal functioning.

In the neuropsychological literature, there are many descriptions of clinical conditions in which the belonging of one’s own limb to the body is questioned. A well-known neuropsychological syndrome that emerges from neural damage to the networks dedicated to the representation of the space surrounding the body (i.e., peripersonal space) is *unilateral spatial neglect* (commonly known as neglect; N+ patients). A peculiar form of neglect, i.e., *personal neglect* (PN), consists in losing the awareness of the contralesional body parts (Caggiano & Jehkonen, 2018). Hence, PN+ patients are still able to explore the contralesional peripersonal space but fail to explore the contralesional body parts. If the examiner tries to bring the patients’ attention towards the affected body side, PN+ patients ignore the questions and, if instructed to touch with the unaffected hand the affected one, they never reach the target, often stopping at the chest. However, they appear as satisfied with their performance as if they actually completed the task. In addition to the lack of exploration, there is often a subtly different behaviour that implies also an explicit denial of ownership towards the affected body part, which was termed *asomatognosia* by Critchley (Critchley, 1953). Such disturbance includes abnormalities in various facets of body representation such as the experienced existence, visual self-recognition, and sense of belonging of contralesional body parts (Jenkinson et al., 2018). For these patients, the affected body part seems to have "vanished from consciousness” and becomes a useless object, forgotten and unused

(Benke et al., 2004). As a consequence, those hands and arms are considered as if they never existed and the patients lose any subjective experience regarding them. In addition to the lack of exploration of one side of the body (PN), the explicit denial that a limb belongs to one's own body (asomatognosia), one of the most unexpected observed behaviours is the attribution of the denied body parts to others (i.e., *somatoparaphrenia*). Interestingly, this feeling of disembodiment has been described not only at the behavioural but also at the physiological level, with decreased anticipatory responses to threat towards the affected (but not the unaffected) hand (Romano et al., 2014).

To sum up, these pathological conditions, which represent only some examples of the variety of body ownership disturbances that can follow brain damage, suggest the existence of a complex neural dynamic that is responsible for the creation of an accurate sense of body ownership under normal conditions. Consequently, a challenge for cognitive neuroscience is to understand the mechanism through which our brain computes a coherent the sense of body ownership.

Previous influential models assumed a central role of multisensory integration processes. According to these accounts, the realignment of afferent inputs coming from different sensory modalities into a common reference frame is a necessary prerequisite in order for the sense of body ownership to occur (Blanke et al., 2015; Serino, 2019). Since the own body is the only object in the world which can be, for instance, seen and perceived in the exact same location and at the exact same time, the convergence of visual and proprioceptive afferences should continuously inform our brain about our body boundaries (Fossataro, Rossi Sebastiano, et al., 2020). Based on this principle, researchers have developed specific procedures able to modulate the sense of body ownership in healthy participants. Among the experimental procedures, the *rubber hand illusion* [RHI; (Matthew Botvinick & Cohen, 1998b)] represents the most frequently employed one. Its classical version, the *visuo-tactile RHI*, consists in stroking the participant’s concealed hand synchronously with a visible dummy arm, positioned in a body-congruent way from the participant’s egocentric perspective (see Fig. 2 below). After about 10 seconds (della Gatta et al., 2016), the experimental subject starts to feel as if the fake hand belonged to their own body, (i.e., the so-called “embodiment”) and as if their hand did not belong to their own body anymore (i.e., the so-called “disembodiment”). This feeling can be measured both explicitly, with the employment of devised Embodiment and Disembodiment questionnaires (Longo et al., 2008), or implicitly by measuring the drift of the own hand’s felt position towards the embodied fake one [i.e., proprioceptive drift; (Tsakiris & Haggard, 2005)].

The mechanism underpinning this illusion relies on multisensory integration processes, since our brain is trained to recognise the object on which visual and tactile inputs converge as “own body”. Indeed, during the RHI, the somatosensory afference informs the brain that tactile stimuli are being administered on the own hand (hidden from view), while the visual input informs the brain that the touches are being applied on the fake one. This creates a violation of the “natural rule” according to which, when touch is felt while it is congruently seen on an object, that object is the own body. According to the predictive coding account a neural mechanism that attenuates somatosensation in favour of vision is triggered, in attempt to restore a stable and coherent body representation, leading to the misattribution of the fake hand to the own body (see Chapter 3 for a more extended discussion of this mechanism).

In a similar vein, the *moving RHI*, relies on the contingence of visual and motor inputs to deceive the brain into thinking that a fake hand, which moves in synchrony with the participant’s (unseen) one, is the own hand (Kalckert & Ehrsson, 2012). Again, this illusion is based on the notion that when an object is moving according to my own movements, that object must be my hand. Even if healthy individuals are still able to cognitively recognise that the seen hand is not the own, they report the odd feeling that the fake hand belong to their own body and, concomitantly, they feel as if their real hand did not belong to their body anymore. A peculiar aspect of the moving RHI is that it can also give insight on the relationship between body ownership and the sense of agency [i.e., the feeling of being the agent of the own actions; (Haggard & Chambon, 2012)], because the participant incorporates not only the fake hand but also its movements.

Over the years, many variants of the RHI have been developed according to various experimental demands [e.g., *virtual hand illusion* (Slater et al., 2008); *full-body illusion* (Lenggenhager et al., 2007); *invisible hand illusion* (Guterstam et al., 2013); *cardiac hand illusion* (Suzuki et al., 2013)], but the core mechanism which triggers the feelings of embodiment and disembodiment is always based on the same principle, that is multisensory integration.

According to neuroimaging studies conducted on both human (Botvinick, 2004; Ehrsson et al., 2005; Makin et al., 2008; Grivaz et al., 2017) (see Fig.1) and non-human (Graziano et al., 2000; Graziano, 1999) primates, the cortical areas that process body-related multisensory stimuli can be localized in premotor and parietal regions, such as the human ventral premotor cortex and the intraparietal sulcus. In line with these works, a series of neuroimaging studies have highlighted a greater activation of parieto-premotor multisensory cortices during the rubber hand illusion, suggesting that high-order cortices may be responsible for the settlement of the visuo-tactile conflict which triggers the body ownership alteration (Brozzoli et al., 2012; Casula et al., 2022; Ehrsson et al., 2004, 2005; Gentile et al., 2015; Golaszewski et al., 2021; Limanowski & Blankenburg, 2015; Petkova et al., 2011).

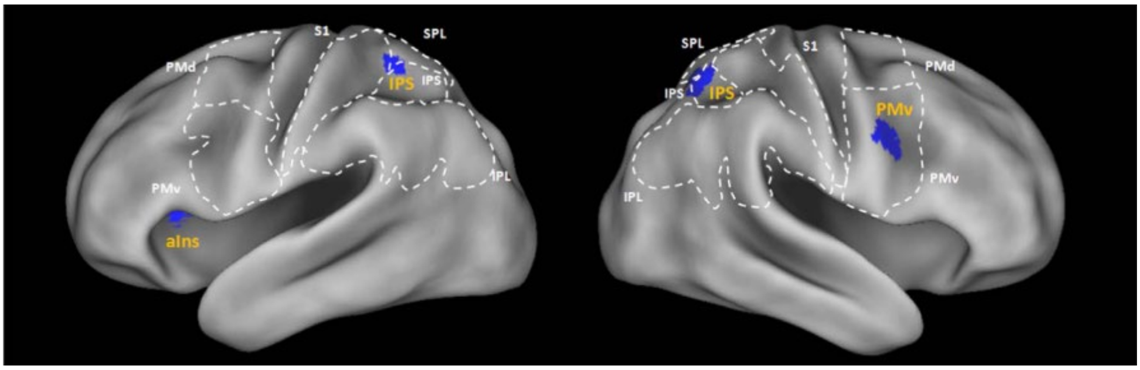


Fig. 1. This figure was taken from Grivaz et al. (2017). Results of the ALE meta-analysis on studies investigating body ownership related networks, employing different versions of the rubber hand illusion (Botvinik & Cohen, 1998). The authors identified 4 clusters: a bilateral cluster located in a parietal region (including left and right intraparietal sulcus – IPS – and superior parietal lobule – SPL – as well as left primary somatosensory cortex – S1), a right cluster in a frontal region (including the ventral premotor cortex – PMv) and a left cluster in the anterior insula (aIns).

Since the principle on which bodily illusions are based is the creation of a multisensory conflict to be settled by such high-order cortices, the classical control condition for the RHI consists in introducing a spatiotemporal asynchrony between the touches delivered to the real and the fake hand, by stroking the two hands in anti-phase. Being tactile and visual stimuli segregated in time and spatial location during the asynchronous condition, multisensory integration mechanisms are not involved. In other words, the scenario of being touched and, in a separate instance, observing touch onto an external object is not in contrast with common experience and does not require a plastic adaptation to restore a coherent bodily representation. Hence, asynchronous stimulation should not trigger the neural mechanism which realigns somatosensation on vision, causing the feeling of embodiment towards the fake limb.

In addition to the asynchronous condition, other controls have been implemented, revealing that also top-down mechanisms are at stake in the elicitation of bodily illusions. For instance, if the to-be-embodied object is not hand-shaped or if it is presented in an implausible position with respect to the participant's body, the illusion cannot be triggered (Blanke et al., 2015). It appears that, in order to be incorporated into one's own body, the external object must follow some precise rules, being endowed with specific characteristics and placed in a specific position. This, rather than being a mere methodological detail, bears a crucial theoretical meaning. It suggests that the implicit process that allows a coherent sense of body ownership emerges from the interplay between bottom-up multisensory integration with a top-down set of prototypical body representation constraints (Garbarini et al., 2020; Tsakiris, 2010). The comparison between the actual state of the to-be-embodied object with a set of constraints defining how its state should be results in the ownership judgement. This mechanism should allow to discriminate between what can or cannot be considered as part of one's own body, based on specific constraints that have been consolidated throughout life by observing sensory regularities (Bertoni et al., 2021). This set of rules, representing a standard body configuration on which, from time to time, our brain relies to distinguish the own body from the others', include three main constraints. First, one's own body parts must match the whole body posture and cannot be placed incongruently with it as, for instance, in allocentric perspective (*proprioception* constraint; see Fig. 2 panel A). Second, one's own body parts must have a human-like shape (*body-related visual information* constraint;

see Fig. 2 panel B). Finally, one's own body parts are located in the space near the body and cannot be placed far away from it (*peripersonal space* – PPS – constraint; see Fig. 2 panel C) [for a review see (Blanke et al., 2015)]. Previous evidence identified the temporo-parietal junction's activity as crucial in selecting what can be potentially included in one's own body suggesting this cortical area as the neural underpinning of such a top-down mechanism (Tsakiris et al., 2008).

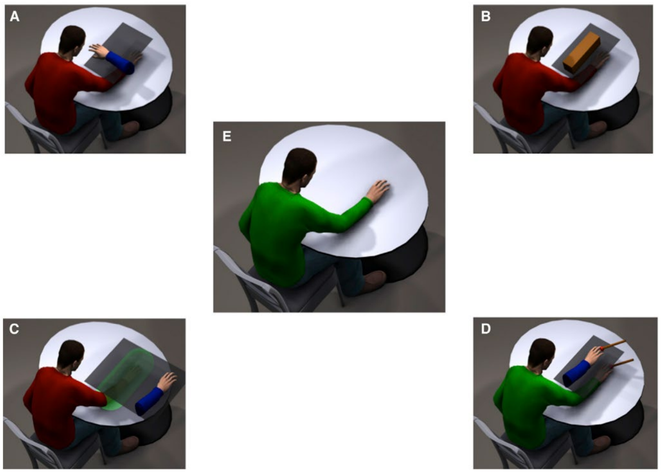


Fig. 2. This figure was taken from Blanke et al. (2015). Embodiment does not occur if: the fake hand is placed in an non-matching body posture ([A], proprioceptive constraint), the object has a non-bodily shape ([B], body-related visual information constraint) or if the artificial hand is presented outside the PPS of the real hand ([C], PPS constraint). Finally, the RHI is effective only if the stroking between hands is synchronous ([D], embodiment constraint). Note that, normally, the self-body matches all of these constraints, leading to a normal sense of body ownership (E). Red and green t-shirt of the participant indicates, respectively, absence or presence of embodiment for the seen object.

The importance of body ownership constraints is even more evident when it comes to neuropsychological syndromes characterized by body ownership disturbances. An interesting pathological model within this context is *pathological embodiment* (Garbarini et al., 2020). Patients affected by pathological embodiment (E+) selectively misidentify an alien hand as their own whenever that hand respects the body ownership constraints. During the clinical evaluation (see Fig. 3), an alien hand (the co-examiner's one) is placed on the table, next to the patient's contralesional affected hand, aligned with the patient's shoulder and perceived in egocentric perspective. Whenever the examiner's hand is located in this body-congruent position, these patients misattribute the alien hand to themselves and they treat and care for it as if it was their own. Hence, when asked to identify the object which lies above their own hand, they report the object which is localized above the alien limb, and when instructed to reach the affected own hand with the unaffected one, they reach and touch the alien one.

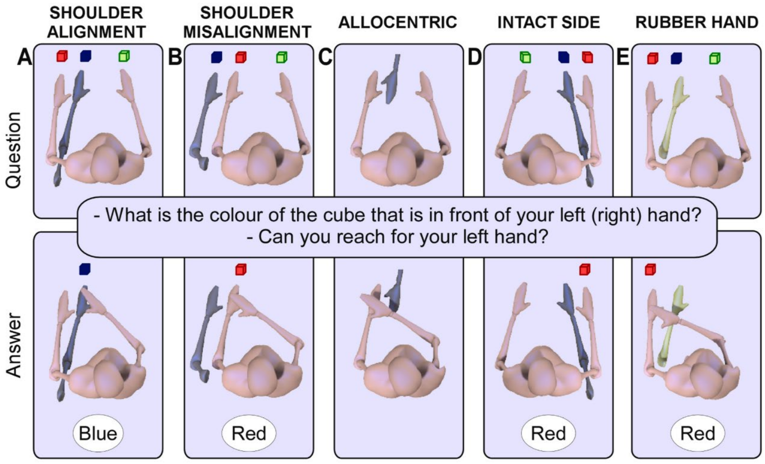


Fig. 3. This figure was taken from Garbarini et al. (2020). Schematic representation of the clinical evaluation of pathological embodiment. In the verbal task, patients are asked to identify their affected (left) hand by naming the colour of the cube in front of it. In the motor evaluation, they must identify their affected (left) hand by reaching it with their unaffected (right) hand. Only in condition A, where the body ownership constraints are met, E+ patients misidentify the alien hand as their own, while in B, C and E patients correctly identify their left hand and no embodiment occurs. In D, the request is to verbally identify their intact (right) hand (not the left affected one), and right brain-damaged patients responds correctly. The motor evaluation, to reach the intact ipsilesional hand, is usually not performed due to the paralysis of the contralesional (left) limb often associated with pathological embodiment. Please note that in E+ patients with left hemisphere damage the setting and the resulting responses are reversed.

By contrast, this pathological behaviour does not occur when the alien hand is misaligned with the patient's shoulder or when it is perceived in allocentric perspective (see Fig. 3). In other words, the constraints of a prototypical body representation, defining what can/cannot be accepted as a part of the own body, must be respected in order for pathological embodiment to occur (Garbarini et al., 2020; Pia et al., 2020). The most surprising aspect of this counterintuitive behaviour is that, even if E+ patients can discriminate the objective appearance of the alien and the own affected hand as dissimilar (i.e., they can tell the difference in age, sex, colour and shape), however they do not use identity-related visual details to discriminate between what pertains or not to the own body. They seem to rely only on the constraints described above to formulate their ownership judgement.

Even if E+ patients behaviour recalls that of the healthy participants undergoing the RHI some differences between these two models have to be highlighted (see Fig. 3).

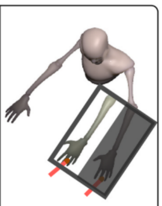
	**PE** *vs* **RHI**	
✓	Peri-personal space (PPS) constraints	✓
✓	Postural and proprioceptive constraints	✓
✓	Body-related visual information constraints	✓
✗	Experimental procedure	✓
✓	Brain damage	✗
✗	Artificial hand	✓
✓	Conscious belief	✗

Fig. 3. This figure was taken from Garbarini et al. (2020). The figure shows analogies and differences between pathological embodiment (PE; left side) and illusory embodiment resulting from the RHI (right side). The green "v" represents what is able to induce embodiment, whereas the red "x" represents what does not.

There are three aspects which fundamentally differ between them. First, in order to induce the RHI, the experimental procedure must be administered, in which visual and real touches are simultaneously delivered to the fake and the real hand and the latter must be covered from view. Conversely, pathological embodiment emerges spontaneously, without any experimental procedure and with both the alien and the patient's hands in full view. Note that, the multisensory integration process is typically detrimental in E+ patients, since pathological embodiment is frequently associated with motor and tactile primary deficits and always associated with proprioceptive deficit (see Fig. 6 at the end of the chapter). Hence, while the ownership judgement is based on both body ownership constraints and spatiotemporal alignment of bottom-up multisensory stimulation in the RHI, it relies only on body ownership constraints in pathological embodiment.

The second, and probably the most obvious, difference is that patients affected by pathological embodiment show the abnormal behaviour due to a brain-damage, whereas the RHI can be induced in healthy participants. Recently, we investigated the cerebral underpinning of this disorder, using three different approaches based on diffusion tensor imaging (Errante et al., 2022). Indeed, previous voxel-based lesion symptom mapping suggested that pathological embodiment could be a disconnection syndrome, emerging from damages to the white matter that links anterior and posterior brain regions (Pia et al., 2020). First, we reconstructed the disconnectome maps in a large sample (N=70) of stroke patients with (E+) and without (E-) pathological embodiment. Second, we leveraged probabilistic tractography, performed on the age-matched healthy controls (N=16), to trace cortical connections that could be damaged E+ and spared in E- patients. Finally, we capitalized on probabilistic 'in vivo' tractography on two E+ patients one E- patient with matched neuropsychological profiles. The results of the three analyses revealed that the arcuate fasciculus and the third branch of the superior longitudinal fasciculus are the most frequently damaged white matter tracts in E+ patients, indicating that pathological embodiment emerges from the disconnection between frontal, parietal and temporal areas (see Fig. 5).

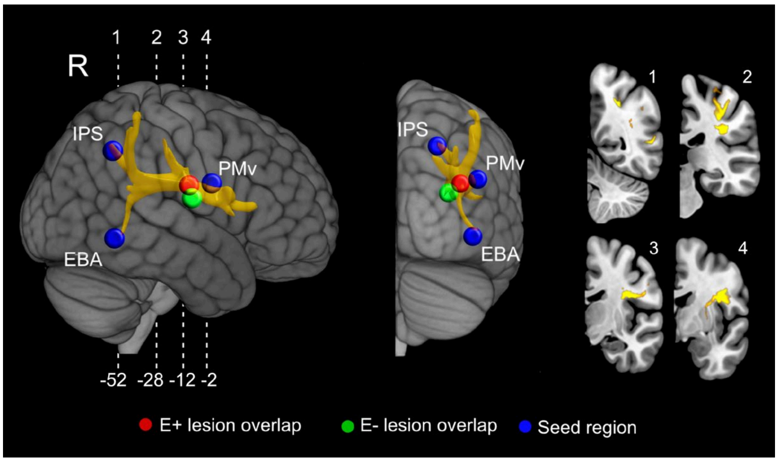


Fig. 5. This figure was taken from Errante et al. (2022). Representation of the white matter tracts which are more frequently lesioned in the E+ with respect to the E− patients. The tract results from the regional

subtraction between the normalized and thresholded fiber tracts reconstructed using the E+ and E− lesions as waypoints. Seeds were decided based on the literature (Downing et al., 2001; Grivaz et al., 2017). The results of this study pinpoint that a large connectivity network encompassing frontal (PMv), parietal (IPS) and occipito-temporal (EBA) regions is involved in the construction of a coherent sense of body ownership

In particular, we proposed that what is crucial here is the disconnection between the ventral premotor cortex, that is known to be implicated in the sensorimotor representation of the body action, and the extrastriate body area, known to be implicated in the visual representation of the body form. Interestingly, a previous neuropsychological study of Moro et al. described a double dissociation between brain lesions in ventral premotor cortex, leading to visual agnosia for the body action, and lesions in the extrastriate body area, leading to visual agnosia for the body form (Moro et al., 2008). Consistently, we proposed that a lesion involving the connection between fronto-parietal sensorimotor regions (including the ventral premotor cortex and the intraparietal sulcus) and temporal visual areas (such as the extrastriate body area) can lead to a form of visual agnosia of the body self, since the bodily-self representation relies on the association between visual and sensorimotor representations of the body (Ferri et al., 2012; Frassinetti et al., 2011).

Besides the brain damage, a third crucial difference between the RHI and pathological embodiment is that, while the former can be induced with a non-biological rubbery dummy, E+ patients show the counterintuitive behaviour only when the alien hand is a biological one (Rossi Sebastiano, Poles, et al., 2022). This aspect is interesting because it informs us that, in E+ patients, the categorization between biological and non-biological objects is preserved and that they present a deficit only when biological stimuli are involved (Candini et al., 2022).

Finally, we mentioned before that healthy participants undergoing bodily illusions still remain cognitively aware that the fake hand is not their own, but they experience what is often reported as an “odd feeling” of embodiment towards the fake hand and a concomitant feeling of disembodiment of the own one. On the contrary, E+ patients are firmly convinced that the alien hand belongs to their own body and report a conscious belief of owning that hand. This difference explains why, when the pathological model is employed to investigate some embodiment-dependent modulations over other domains, the effects are more dramatical, as compared to the effects observed leveraging the RHI. However, employing the illusion procedure on healthy participants bears other not negligible advantages, such as the possibility of administering longer protocols, thus collecting a higher number of trials, given that compliance is usually greater in healthy participants as compared to brain-damaged patients.

To sum up, in order to study the sense of body ownership, scientists have leveraged two complementary research strategies. On the one hand, they employed pathological conditions, such as somatoparaphrenia or pathological embodiment. On the other hand, they employed experimental paradigms able to alter the sense of body ownership in healthy participants. Since the present dissertation has the objective of investigating how the sense of body ownership interacts with motor and sensory perception, a series of studies on this topic will be described, in which both research strategies were employed.

By testing a great cohort of stroke E+ and E- patients, we believe that we previously elucidated that the sense of body ownership does not simply emerge from sensory and motor perception. In particular by comparing the clinical features of E+ and E- patients, we demonstrated double dissociations between pathological embodiment and motor and sensory deficits (Garbarini et al., 2020; Pia et al., 2020). In other words, although primary deficits are frequently associated with pathological embodiment, there are E+ patients without sensory and motor impairment, as well as E- patients with such deficits (see Fig. 6). The only primary deficit which is always associated with pathological embodiment is proprioception impairment. However, it is indeed possible to isolate the body ownership disturbance by matching E+ and E- samples for primary (including proprioceptive) and cognitive deficits, to describe this pathology both behaviourally and neurologically (Errante et al., 2022; Pia et al., 2020).

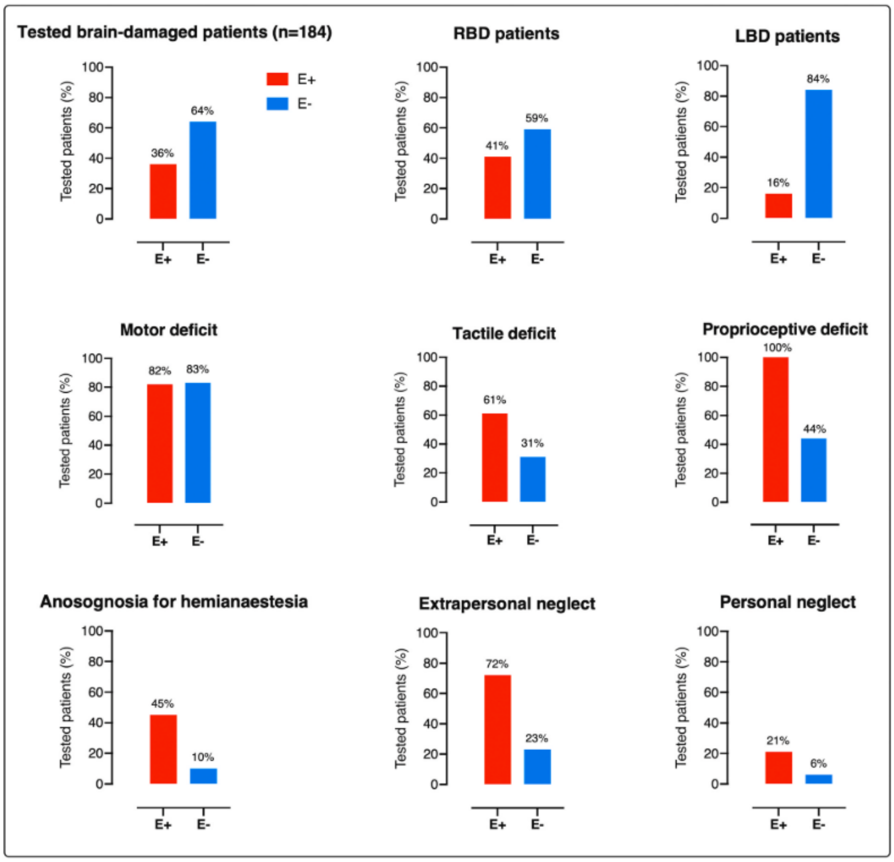


Fig. 6. This figure was taken from Garbarini et al. (2020). The figure represents for both E+ (red) and E− (light blue) patients the percentage of tested patients and their clinical features. See Garbarini et al. (2020) for an extended description of the tests employed for both neurological and neuropsychological characterization.

Having determined that the sense of body ownership cannot be considered as a simple collection of motor and sensory perceptions, we moved the research question to the definition of the relationship between them. To this aim, in the following chapters, I will specifically address whether an alteration of the sense of body ownership generates an alteration of motor control (Chapter 2) and sensory perception (Chapter 3).

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Chapter 2

The relationship between the sense of body ownership and motor control

The relationship between the sense of body ownership and motor control is an interesting topic which has raised a wide debate in the neuroscientific community. Some evidence suggested that, during the RHI, disembodiment may induce a down-regulation of the motor system (della Gatta et al., 2016; Isayama et al., 2019). Coherently, a motor system downregulation may enhance RHI effects (Fossataro, Bruno, Giurgola, et al., 2018). Conversely, recent studies found that the RHI does not interfere with reaction time, acceleration, and velocity of rapid index finger abduction (Reader et al., 2021; Reader & Henrik Ehrsson, 2019).

Even though the RHI ability to modulate the features of basic movements is still under debate, neuropsychological evidence in brain-damaged patients suggests that the incorporation of an alien limb bears profounds effects in E+ patients' motor system (Garbarini et al., 2013, 2015; Irene Ronga et al., 2019). Given the frequent comorbidity between motor deficits and pathological embodiment, Garbarini and colleagues tested E+ patients with full hemiplegia of the contralesional hand to address whether the embodiment of an alien hand resulted in the incorporation of its motor properties as well. Hence, in these studies, movements were performed by the alien (embodied) hand while the patients' hand remained still. The results highlighted that E+ patients not only incorporate a static alien hand in their body representation but also ascribe its movements to their own body. Indeed, during a modified version of a bimanual circle-lines task, they showed significant interference effects of the alien arm movements drawing circles on the actual movements of the intact arm drawing lines (Garbarini et al., 2013). In other studies, the embodiment of the alien arm movement has been shown to induce objective consequences on the perceived length of the paralyzed arm, after tool-use training performed by the alien hand (Garbarini et al., 2015), and on the hemispatial neglect improvement, after prismatic adaptation training [again performed by the alien hand; (Irene Ronga et al., 2019)]. More recently (Rossi

Sebastiano, Romeo, et al., 2022), we described an electrophysiological counterpart of the incorporation of the alien hand's movements into the patients' motor system capitalizing on mu desynchronization, a well-known index of sensorimotor cortices' activity during both movement execution and observation (Angelini et al., 2018). Two E+ and three E- (control) hemiplegic patients underwent a motor observation task either with the alien hand in a body-congruent (internal) position, eliciting pathological embodiment in the E+ group, or in a body-incongruent (external) position, not eliciting embodiment neither in the E+ nor in the E- groups. Patients passively observed an alien hand performing reach-to-grasp movements, in either internal or external positions, during EEG recording. Additionally, eighteen healthy controls underwent the same observation task and also an execution version, in which they performed the reach-to-grasp movements them-selves, while a resting alien hand was placed either in the internal or in the external position. Healthy controls showed greater mu desynchronization in execution than observation, regardless of the hand position. Interestingly, in the observation task, only E+ (and not E-) patients showed a significantly greater desynchronization in internal than in external condition, resembling the difference between execution and observation in healthy controls. This finding provide electrophysiological evidence suggesting that the belief that a moving hand belongs to one's own body triggers a motor system activation as if movements were performed by the own hand.

All these effects were investigated focusing on the movements of the alien - and not the patient's - hand. In other words, the previously mentioned studies investigated the amount of motor system activation while an embodied alien hand moves, either in experimental or in pathological contexts. Here, we aimed to address the complementary issue of how movements are performed focusing on the patient's hands. More specifically, our research interest was twofold. First, in Study 1.1 (Rossi Sebastiano, Poles, et al., 2022), we sought to establish whether the motor system programs movements with the hand which is physically attached to the own body (the real hand) or with the hand which is believed to the one's own (the alien hand). Second, in Study 1.2 (Errante et al., *in preparation*), we explored whether, following the RHI, self-directed movements aimed to the deceived body part are performed taking into account the real or the fake hand as a target. Crucially, in this study, to test whether this illusory embodiment is able to deceive not only humans, but also the non-humans primates, we tested a monkey with the very same paradigm employed in the cohort of humans.

Study 1.1: Reach planning with someone else's hand

[This research has been published in Rossi Sebastiano A., Poles K., Miller L.E., Fossataro C., Milano E., Gindri P., Garbarini F. (2022) Reach planning with someone else's hand. Cortex. 10.1016/j.cortex.2022.05.005]

Introduction

Recent studies have suggested that the illusory feeling of embodiment modifies the reaching vector of the physical arm (Fang et al., 2019; Zopf, Truong, et al., 2011). In other words, while the movement itself may not be affected by embodiment (Reader et al., 2021; Reader & Henrik Ehrsson, 2019), the hand from which the movement is programmed might be switched to the incorporated hand, during the RHI. For instance, Zopf and colleagues (Zopf, Truong, et al., 2011) demonstrated that reaching trajectories are significantly shifted towards a rubber hand only after synchronous visuo-tactile stimulation of the participant's hand and the rubber hand, i.e., the condition wherein embodiment towards the fake limb was reported. In a similar vein, Fang and colleagues (Fang et al., 2019) leveraged a video-based version of the moving rubber hand illusion (Kalckert & Ehrsson, 2012), finding that reaching movements' trajectories are more attracted toward a visually displayed arm under moderate multisensory conflict, i.e., the condition wherein they are more likely to ascribe the visual arm to their own body.

However, other studies have argued that there may be a dissociation between the incorporation of a limb at the explicit level – measured via embodiment questionnaires – and at the implicit level – measured via reaching and/or proprioceptive drift. For instance, Rhode and colleagues demonstrated that proprioceptive drift can result both from the simple visual exposure to a prosthetic hand and from the synchronous (but not asynchronous) stroking of the fake and the participant's hand, whereas embodiment is elicited only in the synchronous RHI condition (Rohde et al., 2011). Their finding indicates that the embodiment condition might be sufficient but not necessary to elicit proprioceptive drift. Conversely, Newport and colleagues found that, when two dynamic hands moved synchronously with their own, participants explicitly reported embodiment over both hands, but programmed movements only from the position of the hand nearer to the body midline (Newport et al., 2010). This interesting study suggests that synchronicity produces embodiment independently from the hand's position. On the other hand, besides synchronicity, the hand's position seems crucial for proprioceptive drift to emerge. In other words, the embodiment condition might be necessary but not sufficient to elicit a reaching drift.

To sum up, at present there is no consensus about the role of body ownership in motor planning and previous studies show mixed results. However, all the aforementioned research relied on participants with spared position sense, representing a potential confound for truly testing the effect of embodiment on reaching. When proprioception is spared, movements are largely planned based on the proprioceptive estimation of the own hand position and thus it is difficult to draw conclusions on embodiment-dependent effects without stumbling on proprioceptive confounds. To overcome these limitations, the present study tested three brain-damaged patients affected by a complete proprioceptive loss, two with and one without pathological embodiment. The proprioceptive deafferentation in these patients allowed us to address the role of body ownership in reaching, in absence of proprioception-related confounds.

In the first experiment (Experiment 1), an E+ patient (E+1), a well-matched control patient without pathological embodiment (E-), and a control sample of age-matched healthy individuals underwent a memory-guided reaching task. In the task, they had to reach for a target from a fixed starting point in absence of vision, after having been presented with either an alien (the co-experimenter's) or a rubber hand aligned with the shoulder, to the right of the patient's hand. Note that, as stated in Chapter 1, pathological embodiment emerges only when a biological alien hand – not a rubbery dummy – is aligned with the shoulder (closer to the body) and the patient's hand is externally positioned. When the position of the two hands is switched (i.e., the patient's hand is closer to the body) pathological embodiment does not emerge and patients show residual capacity to correctly identify their own hand (Pia et al., 2020). In the present study, we decided to replace the examiner's hand with a rubber hand in the control condition, so that the initial position of reaching movements was the same as in the experimental (alien) condition.

Accordingly, irrespective of proprioception damaged in both patients, only in the E+ patient, a greater attraction of the movement vector was expected towards the alien hand as compared to the rubber hand. Furthermore, we performed a second experiment (Experiment 2) wherein another E+ patient (E+2; with the same neuropsychological profile of E+1) was recruited to take part in both the *memory guided* task described above, and a *visually guided* version of the reaching task (with a visual feedback of the target). The aim of Experiment 2 was to investigate whether the effect found in Experiment 1 could be generalized to other forms of reaching, or if it is specific to memory control.

Finally, to corroborate the neuropsychological evidence highlighted by the single-case studies, we designed an additional experiment (Experiment 3), in which we specifically investigated whether the magnitude of reaching errors committed by healthy participants subjected to the RHI were related to the degree of illusory embodiment of the alien limb and disembodiment of one's own arm.

Materials and Methods

Participants

Experiment 1 & 2: single-case studies

Cases Description. The E+1 patient was a right-handed (R. Oldfield, 1971), seventy-two year old man, who was admitted to the San Camillo Hospital following a cerebrovascular accident (ischemic stroke) which happened in February 2019. At the time of this study, he had already been dismissed from the hospital and had completed the rehabilitation. According to the neuropsychological/neurological evaluation, this patient represented a very interesting E+ case for the purpose of this study since he showed completely spared motor function and proprioceptive deafferentation of the left (contralesional) limb. According to previous studies [e.g., (Pia et al., 2014; Piedimonte et al., 2016; Ricci et al., 2016)], motor and tactile functions, as well as general cognitive impairment, personal and extrapersonal neglect were assessed through standardized neurological protocols. As in previous studies (Fossataro et al., 2018; Fossataro et al., 2017), proprioception was assessed by means of two evaluation protocols for testing the limb localization: the Contralateral Limb Matching Task [CLMT (Goble, 2010; Lincoln et al., 1991; Piriyaprasarth et al., 2009)] and the Finger Localizing Test [FLT (Head & Holmes, 1911; Hirayama et al., 1999; Lincoln et al., 1991)]. To evaluate the presence/absence of pathological embodiment we employed a previously devised protocol (Garbarini et al., 2020; Pia et al., 2020). For an extended description of the pathological embodiment evaluation, see the paragraph below. This patient presented a wide-spread fronto-parietal cortical and subcortical damage, identified by means of MRI scans.

To isolate the alien limb embodiment from the proprioceptive-related confound, we selected a well-matched control patient with proprioceptive deficit and without pathological embodiment (E-), whose evaluation revealed a similar neuropsychological/neurological profile (E-; see Table 1 for clinical details). This patient presented an extended parieto-temporo-occipital cortical and subcortical damage to the right hemisphere.

The E+2 patient that took part in Experiment 2 was selected to match the E+1 characteristics as closely as possible (see Table 1 for clinical details). According to the neuropsychological/neurological evaluation, this patient showed completely spared motor function and proprioceptive deafferentation of the left (contralesional) limb. This case presented an extended fronto-parietal cortical and subcortical lesion in the right hemisphere. The extent of the lesion volume was comparable among the three cases.

	E+1 case	**E+2 case**	**E- case**
Sex	M	M	M
Age	72	89	57
Education	13	13	13
Onset	475	142	490
MoCA	19	20	21

Proprioceptive deficit	+	+	+
Hemiplegia	–	–	–
Hemianesthesia	–	–	–
Extrapersonal neglect	+	+	+
Personal neglect	+	+	+

Table 1 Patients' clinical data. M=male; F=female; Education=years of school; Onset=days between the disease and the first assessment. Global cognitive assessment was performed using the Montreal Cognitive Assessment [MoCA; cutoff ≥17; (Bosco et al., 2017)]. Presence/absence of deficit is indexed as +/–. Extrapersonal neglect was assessed with the Behavioural Inattention Test, including conventional and behavioural subtests [BIT; cutoff ≥129; (Wilson et al., 1987)]. Personal neglect was assessed with the Fluff test [cutoff omissions L ≥2; (Cocchini et al., 2001)].

Pathological Embodiment Evaluation. The patient's hands were comfortably placed on the table, palms facing down. The evaluation comprised: i) an experimental condition, wherein the co-experimenter's gender-matched left hand (i.e., *alien hand*) was placed in a body-congruent position; ii) a control condition, wherein the alien hand was replaced by a fake gender-matched left hand (i.e., *rubber hand*). In both conditions, the additional (alien/rubber) hand was aligned with the patient's left (contralesional) shoulder and in egocentric perspective, whereas the patient's left hand was misaligned with the shoulder, 20 cm to the left of the additional hand. At the beginning of the evaluation, three 5x5 cm wooden cubes (blue, green and red) were respectively placed in front of the additional, the patient's right and the patient's left hands. Before the evaluation began, the patient was preliminarily asked (three times) to verbally report the number of arms on the table (i.e., one, two or three) and to name the color of three cubes (blue, green and red). In order to participate in the experiment, the patient had to be errorless in counting the arms and in naming the color of the cubes (i.e., if neglect prevented the perception of these stimuli, the patient could not be included in the study). Then, the experimenter placed one cube in front of each hand present on the table (at a distance of approximately 5 cm) and asked the patient "*What is the color of the cube that is currently in front of your left hand?*" **(Q1)**. Then, the experimenter changed the cube positions and started another trial. These trials were administered eight times within each condition and the percentage of times the patient reported the block in front of each hand was recorded. Finally, the experimenter removed the cubes and asked the patient "*Could you reach for your left hand?*" **(Q2)** for a total of eight times within each condition, and the percentage of times the patient reached for each hand was recorded. The E+ patients (E+1 and E+2) reported the cube in front of the alien hand **(Q1)** and reached for that hand **(Q2)** 100% of the times in the alien hand condition, whereas they reported the cube in front of their own hand **(Q1)** and reached for their own hand **(Q2)** 100% of the times in the rubber hand condition. The E- patient reported the cube in front of his own hand **(Q1)** and reached for his own hand **(Q2)** 100% of the times in both the alien and the rubber hand conditions. The evaluation was repeated before each session of the present study (see *Experimental procedures* below).

Control group. To compare the E+1, E- and E+2 performance with reference to a normative sample, we also tested a group of ten age-matched right-handed healthy controls [4 women; age (mean±SD): 64±8; education: 15.5±1.64]. These participants were naïve to the experimental procedure and to the purpose of the study.

Patients (prot.n° 0032276/20 approved by the Ethical Committee of ASLTO1, Turin) and controls (prot.n° 199278/20 approved by the Ethical Committee of the University of Turin) gave informed consent before participating.

Experiment 3: RHI on healthy participants

With the aim to confirm the results of the single-case studies, showing that the (altered) sense of body ownership plays a crucial role in planning a reach, we recruited and additional sample of young healthy participants and investigated whether reaching errors observed during the RHI may be due to changes in ownership. The sample size was a priori determined according to a power analysis applied to the results obtained in a pilot experiment involving ten subjects. The effect size was calculated on the delta between the mean error of the synchronous and that of the asynchronous block (see *Experimental procedures* below). We computed the required sample numerosity to reach a power of 0.9 (dz=0.7, alpha=0.05, actual power=0.9, sample size=20). Thus, twenty healthy participants [13 women; age (mean±SD): 24.95±2.33; education: 16.4±2.04] took part in Experiment 2. They were all right-handed, had normal or corrected-to-normal vision, and were naïve to the aim of the study. Before the experiment, all participants gave informed consent to participate in the study (prot.n° 125055/16 approved by the Ethical Committee of the University of Turin).

Experimental procedures

Experiment 1: memory guided reaching

Experiment 1 was performed to investigate the effect of embodiment on memory-guided reaching. Participants underwent two sessions (i.e., *alien* and *rubber*), both beginning with a baseline block in which their performance at a reaching task was assessed in absence of any cues on the table (i.e., neither the alien nor the rubber hands were present). Then, after the baseline block, participants performed a hand block in which the reaching task was repeated while either the experimenter's (in the alien session) or a fake (in the rubber session) left hand was placed in a body congruent position. Note that, to avoid any long-lasting after effect of embodiment on the reaching performance, the experimental (alien) and the control (rubber) sessions were run in separate days.

In each block, participants sat on a chair with both hands laying comfortably on a desk. A black cloth covered the left shoulder and the proximal parts of the arms so that, in the hand blocks, the discontinuity between the alien/rubber hand and the body was concealed. A black wooden target (5×10×2 cm) was positioned 10 cm in front of the subject's left hand and slightly shifted to the right (10 cm), resulting at equal distance between the alien/rubber and the own hand in the hand blocks. Note that, before each session, a brief training was performed wherein the participants made five reaching movements towards the target with visual feedback, in order to be sure that they were able to successfully complete the movement in absence of any additional hand.

At the beginning of each trial of the reaching task, the participant was asked to look at a central point in between the two hands (i.e., the own and the alien/rubber hand) so that they could have both hands in the visual field for 5 seconds. Then, the experimenter asked to gaze at the target which was always equidistant from both the alien/rubber and the patient's hand. Patients were instructed to perform a ballistic pointing movement towards such target with the left hand, immediately after being blindfolded (see Fig. 7). Hence, the delay between the patient's action planning and movement onset consisted of the time employed by the experimenter to blindfold the patient, i.e., about 2-5 seconds. Note that, to avoid tactile feedback that could have led to online movement's correction, we covered the desk and the target with a plastic film so that participants could never know whether they correctly landed on the block or not. Finally, the experimenter measured the error (i.e., the distance between the movement's endpoint and the target, with negative values indicating leftwards errors), moved the hand back to the starting position, and removed the blindfold.

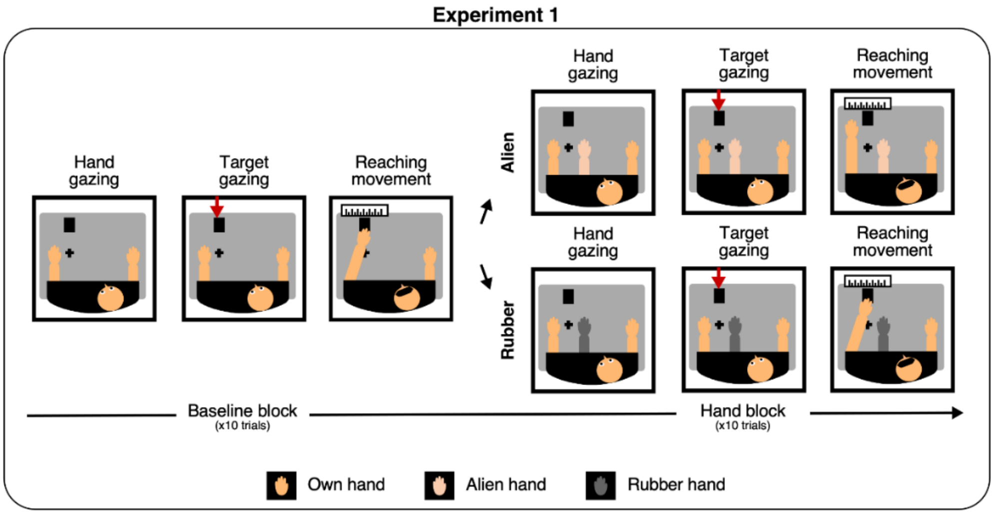

Fig. 7 Experimental procedures of Experiment 1. Participants underwent 2 sessions, both beginning with a baseline block (no hand present), followed by a hand block (either the alien or the rubber hand present, according to the session). Each block consisted in 10 trials of the reaching task. At the beginning of each trial, the participant looked at a central point between the left hands for 5 seconds (hand gazing). Then, the experimenter indicated the target to draw the patient's attention on it (target gazing) and, after she put the blindfold on the patient's eyes (2-5 seconds), the patient performed a reaching movement toward the target

(reaching movement). Then, the experimenter measured the mean error and, after having relocated the patient's hand on the starting position, removed the blindfold.

Experiment 2: memory and visually guided reaching

Experiment 2 was performed to investigate whether the effect of embodiment on memory-guided reaching demonstrated in the Experiment 1 was also present for on-line reach planning and execution. To this aim, the E+2 underwent both a *memory* and a *visually guided* reaching task, in separate sessions. The memory guided task was identical to that performed by E+1 and E- patients (see the paragraph above). The visually guided task was similar to the memory guided one, except that a custom-made apparatus was employed to hide the hands – but not the target – from view during reaching movements, instead of blindfolding the participant. More specifically, the patient laid the left contralesional hand inside a wooden box whose ceiling was open. A wooden panel was placed on top of the box during the movement to cover the view of the hand. As in the memory guided task, after a baseline block, the patient performed either an alien or a rubber hand block, depending on the session. The task was identical in the baseline and the hand blocks, except that, in the hand block, an additional (alien or rubber) hand was positioned inside the box, 20 cm to the right of the patient's left hand.

At the beginning of each trial, the patient was instructed to look at a central point between the two hands (i.e., the own and the alien/rubber hand) for 5 seconds, then the experimenter indicated the target and, after the box was covered by the wooden panel preventing the view of the hand(s), the patient performed a ballistic reaching movement with the left hand towards the target while gazing at it. Note that, in the visually guided task, the target was moved 20 cm further so that the participant's reaches landed below it, and the hand remained covered from view without giving the participant's visual feedback about the movements' endpoint. Then, the experimenter measured the error (i.e., the distance between the movement's endpoint and the target, with negative values indicating leftwards errors), moved the hand back to the starting position, and removed the panel. Note that, to compare the E+2 patient’s performance to a normative sample, the control group underwent the visually guided task as well.

Experiment 3: RHI on healthy participants

The procedures employed in Experiment 3 were similar to those of Experiment 1, except that we leveraged the RHI (Matthew Botvinick & Cohen, 1998a) to induce healthy participants to experience an illusory feeling of embodiment over an alien hand. Participants laid their limbs on a desk with their left hand covered from view by a vertical panel. The experimenter’s hand (i.e., alien hand) was placed in an anatomically congruent position [i.e., 20 cm to the right of the participant’s hand, as in previous studies (della Gatta et al., 2016; Rossi Sebastiano et al., 2021)] and a black piece of tissue covered the shoulders and the proximal portions of the participant’s hand and the alien hand. The black wooden target was placed in the very same position of Experiment 1. Participants underwent two blocks (i.e., *synchronous* and *asynchronous*) in a counterbalanced order, wherein each trial of the reaching task described in Experiment 1 was preceded by 1 minute of RHI stimulation, during which an alien (visible) hand and the participant’s (hidden) hand were stroked synchronously/asynchronously and participants gazed at the alien hand (see Fig. 8). At the end of each block, participants rated their agreement with the items of the Embodiment and Disembodiment questionnaires [see Table 2 (Fossataro et al., 2018; Longo et al., 2008)].

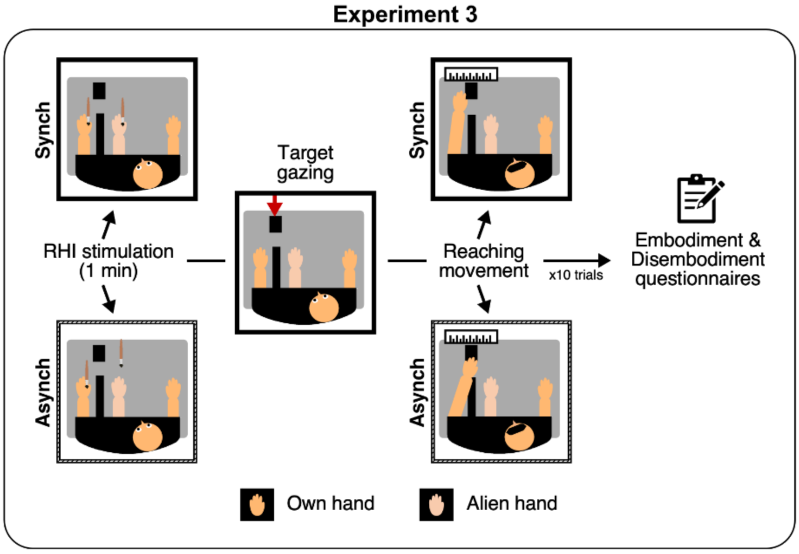

Fig. 8 Experimental procedures of Experiment 3. Participants underwent two blocks (synchronous or asynchronous depending on the RHI stimulation) performed in a counterbalanced order. Each block comprised 10 trials of a reaching task which was identical to that of Experiment 1, except that, before the target gazing, 1 minute of RHI stimulation (synchronous or asynchronous depending on the block) was performed. At the end of each block, embodiment and disembodiment questionnaires were completed.

Embodiment Questionnaire	**1.** It seemed as if I were sensing the touch in the location where I saw the rubber hand touched
	2. It seemed as if the touch I felt was caused by the paintbrush touching the rubber hand
	3. I felt as if the rubber hand was my hand
Disembodiment Questionnaire	**1.** It seemed like I was unable to move my hand
	2. It seemed like I couldn't really tell where my hand was
	3. It seemed like my hand had disappeared

Table 2 Embodiment and Disembodiment Questionnaires (Fossataro et al., 2018; Longo et al., 2008) Participants were asked to rate their agreement with the following statements by assigning a score to each item, using a 7 points Likert Scale (-3 = "strongly disagree"; +3 = "strongly agree").

Finally, we ran a second session with a subset of participants (N=14) in order to more directly assess the role of proprioceptive drift. The experimental session, consisting of two blocks (i.e., synchronous and asynchronous), was performed in a counterbalanced order. Before each block, we covered the hands with a black box and collected ten proprioceptive judgements (Proprioceptive Judgement Pre). A ruler was positioned over the box and participants verbally reported the number on the ruler which corresponded to the felt location of their left index finger. For each proprioceptive judgement, the ruler was positioned on the box so that the number corresponding to its right limit was always different, to avoid that the participant could anchor the judgement on a given number. The experimenter took note not only of the number reported by the participant, but also of the number corresponding to the right limit of the box, and we considered the delta between the two numbers as a proprioceptive judgement. Afterwards, the black box was removed, and the block began. In each trial of the block, 1 minute of RHI stroking (synchronous or asynchronous depending on the block) was performed and, after having covered the hands with the box, a proprioceptive judgement (Proprioceptive Judgement Post) was collected. This procedure was repeated for a total of 10 trials.

Data analyses

Experiment 1: memory guided reaching

For the following analyses, we employed the Crawford Bayesian test (Crawford et al., 2010) that allows investigating whether the difference between two cases is greater than that between a pair of controls. First, we conducted a preliminary analysis to rule out that the E+1 and the E- cases' performance (mean error) differed in the baseline. Second, we compared the mean error of the E+1 and the E- cases separately for the hand block of each session (i.e., the alien hand and the rubber hand condition). Third, we compared the E+1 and the E- cases' performance by computing an error index (i.e., error index = mean error in alien minus mean error in rubber hand block). Finally, to verify whether the modulation of the perception of hand position shifted over the time-course of the experiment when embodiment was present, we plotted the error in each trial of the Alien hand condition.

Experiment 2: memory and visually guided reaching

For the following analyses, we employed the Crawford Bayesian test (Crawford & Garthwaite, 2007) that allows to compare the performance of a single case to that of a normative sample. As in the first experiment, we first tested whether the E+2 case's performance differed from the control group in the baseline block. Second, we compared the E+2 case's performance to that of the control group separately for each hand block (i.e., *alien* and *rubber*) and task (*memory guided* and *visually guided*). Moreover, to verify the presence of a differential effect between the alien and the rubber hand blocks in both tasks, we compared the E+2 and the controls' error index (i.e., error index = mean error in alien minus mean error in rubber hand block) separately for the memory guided and visually guided task. Furthermore, to verify whether the modulation of the perception of hand position shifted over the time-course of the experiment when embodiment was present, we plotted the error in each trial of the Alien hand condition for both the memory and the visually guided tasks.

Experiment 3: RHI on healthy participants

First, we conducted a preliminary analysis to confirm that participants experienced embodiment over the alien hand and disembodiment of their own hand, by comparing the mean ratings attributed to the Embodiment and Disembodiment questionnaires. Since the residuals were not normally distributed (Shapiro Wilk test: $p<0.05$), we employed the Wilcoxon matched pairs test. Second, we investigated the effect of the RHI on reaching performance, by comparing the mean error in the synchronous to that in the asynchronous condition with a Wilcoxon matched pairs test (Shapiro Wilk test on residuals: $p<0.05$). Then, we conducted correlational analyses to verify whether the level of embodiment/disembodiment directly influenced the magnitude of the reaching error. Note that, since the illusion effect is indexed, at the individual level, by differential values between synchronous and asynchronous conditions (Romano et al., 2021), we ran two Pearson correlations (Shapiro Wilk test on residuals: $p>0.05$), respectively between an error score (mean error in the synchronous minus the mean error in the asynchronous condition) and 1) an embodiment and 2) a disembodiment score (both computed as the average rating attributed to the items of the embodiment/disembodiment questionnaire in the synchronous minus that in the asynchronous condition). In both 1) and 2) a negative correlation was expected, indicating that the more the participant felt ownership (of the alien hand) / disownership (of the own hand), the more the error was leftward (values <0), consistently with reach planning from the alien (not the own) hand’s position.

Finally, to verify whether the 1-minute RHI was able to induce proprioceptive drift, we computed the proprioceptive drift on the subset of participants that took part in the second session, by subtracting the mean Proprioceptive Judgement Post to the mean Proprioceptive Judgement Pre, separately for each condition. Then, we compared the proprioceptive drift in the synchronous and asynchronous conditions by means of a Wilcoxon matched pairs test (Shapiro Wilk test on residuals: $p<0.05$).

Results

Experiment 1: memory guided reaching

Our preliminary analysis confirmed that there was no difference between the E+1 and the E- cases' mean error in the baseline, i.e., when they had to reach for the target in absence of the alien/rubber hand [E+1 error (mean)=0.1; E- error (mean)=0; controls' error (SD)=0.62; Z(PCC)=0.11; p=0.91 (two-tailed); see Fig. 9 panel A]. Interestingly, when we analyzed the alien and the rubber hand blocks, we found that the E+1 patient showed a significantly greater leftward bias in his reaching movement (i.e., greater attraction toward the alien/rubber hand as expressed by negative values), as compared to the E- patient [Alien: E+1 error (mean)=-9.2; E- error (mean)=0; controls' error (SD)=0.67; Z(PCC)=-9.72; p=0.000005 (two-tailed); rubber: E+1 error (mean)=-4.6; E- error (mean)=0; controls' error (SD)=0.16; Z(PCC)=-20.33; p=0.000001 (two-tailed); see left and central panel of Fig 9]. Crucially, when we analyzed the error index, computed as the difference of reaching errors between alien and rubber hand blocks, we found that this difference was significantly greater in the E+1 than in the E- patient [E+1 error score (mean)=-4.6; E- error score (mean)=0; controls' error score (SD)=0.65; Z(PCC)=-5.01; p=0.0007 (two-tailed); see right panel of Fig. 9 panel B], with the E+1 patient showing a greater attraction toward the alien (embodied) hand than toward the rubber (control) hand. Note that the plot of the trial progression shows that the error remained constant over the time-course of the experiment, demonstrating that as soon as the E+1 patient saw the alien hand, he immediately recalibrated the movement's starting position (see Fig. 9 panel C).

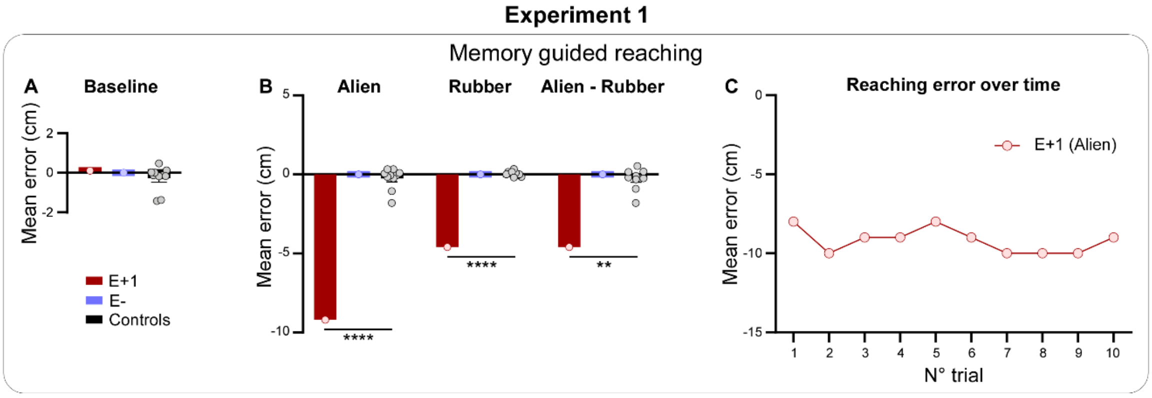

Fig. 9 Results of Experiment 1: memory guided reaching. The plots in A and B represent the mean error of the E+1 patient (in red), the E- patient and the controls (in black) respectively in the *baseline*, in the hand (*alien* and *rubber*) blocks and the error index (mean error in the *alien* – *rubber* hand blocks). The plot in C represents the reaching errors over the time-course of the experiment. Dots represent individual participants. Error bars represent the standard error of the mean (SEM) and asterisks represent the significant differences (**p<0.001, ****p<0.0005).

Experiment 2: memory and visually guided reaching

The first analysis confirmed that there was no difference between the E+2 and control's mean error in the baseline in both tasks [Memory guided: E+2 error (mean)=-1.3; controls' error (mean±SD)=-0.28±0.62; Z(PCC)=-1.65; p=0.151 (two-tailed); Visually guided: E+2 error (mean)=-1.05; controls' error (mean±SD)=-0.04±0.61; Z(PCC)=-1.66; p=0.148 (two-tailed); see Fig. 10 panel A]. As far as the memory guided task is concerned, we replicated Experiment 1's results. Indeed, we found that the E+2 case showed a significantly greater leftward bias in both alien and rubber blocks [Alien: E+2 error (mean)=-11.2; controls' error (mean±SD)=-0.25±0.67; Z(PCC)=-16.34; p<0.000001 (two-tailed); Rubber: E+2 error (mean)=-6.85; controls' error (mean±SD)=0.04±0.16; Z(PCC)=-43.06; p<0.000001 (two-tailed); see Fig. 10 panel B]. Furthermore, the difference of reaching errors between alien and rubber hand blocks was significantly greater in the E+2 than the control sample [E+2 error index (mean)=-4.35; controls' error index (mean±SD)=-0.29±0.65; Z(PCC)=-6.25; p=0.0002 (two-tailed); see Fig. 10 panel B].

Finally, the plot of the trial progression shows that the error remained constant over the time-course of the experiment, replicating Experiment 1's results (see Fig. 10 panel C).

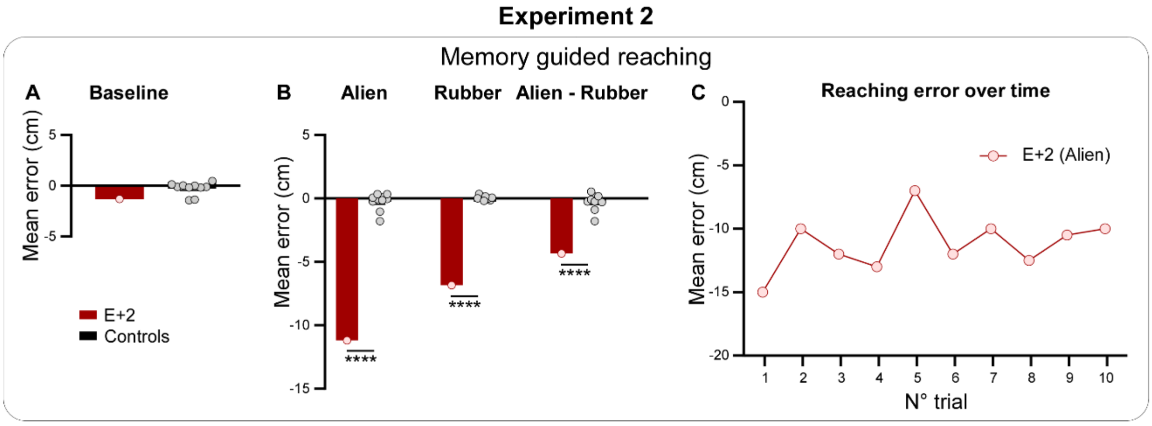

Fig. 10 Results of Experiment 2: memory guided reaching. The plots in A and B represent the mean error of the E+2 patient (in red) and the controls (in black) respectively in the *baseline*, in the hand (*alien* and *rubber*) blocks and the error index (mean error in the *alien* – *rubber* hand blocks) of *memory guided* task. The plot in C represents the reaching errors over the time-course of the experiment. Dots represent individual participants. Error bars represent the standard error of the mean (SEM) and asterisks represent the significant differences (****p<0.0005).

Interestingly, the results of the visually guided task showed the same pattern as the memory guided one. That is, we observed a significantly greater leftward bias in both alien and rubber hand blocks [Alien: E+2 error (mean)=-14.8; controls' error (mean±SD)=-0.19±0.61; Z(PCC)=-23.95; p<0.000001 (two-tailed); Rubber: E+2 error (mean)=-5.1; controls' error (mean±SD)=0.06±0.91; Z(PCC)=-5.67; p=0.0004 (two-tailed); see Fig. 11 panel B] and a significant difference between alien and rubber hand blocks [Error index: E+2 error (mean)=-9.7; controls' error (mean±SD)=-0.3±0.64; Z(PCC)=-14.69; p=0.0000002 (two-tailed); see Fig.

11 panel B]. Furthermore, except for the first trial, the error was constant over time, as in the memory guided task (see Fig. 11 panel C).

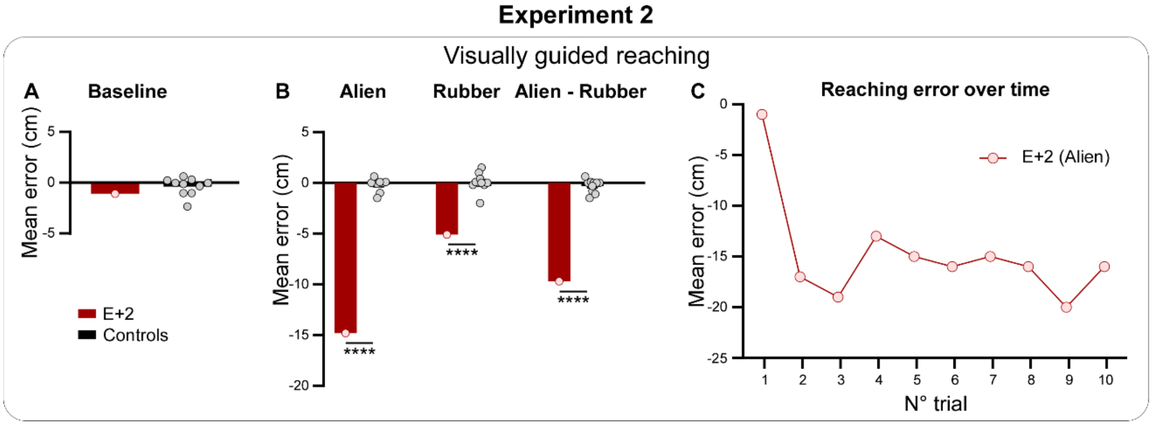

Fig. 11 Results of Experiment 2: visually guided reaching. The plots in A and B represent the mean error of the E+2 patient (in red) and the controls (in black) respectively in the *baseline*, in the hand (*alien* and *rubber*) blocks and the error index (mean error in the *alien – rubber* hand blocks) of *visually guided* task. The plot in C represents the reaching errors over the time-course of the experiment. Dots represent individual participants. Error bars represent the standard error of the mean (SEM) and asterisks represent the significant differences (****$p<0.0005$).

Experiment 3: RHI on healthy participants

The analyses run on Embodiment and Disembodiment questionnaires confirmed that there was a significant difference between conditions, with participants attributing significantly more positive ratings in the synchronous as compared to the asynchronous condition (Embodiment: $t_{19}=0$, $z=3.92$, $p=0.00009$; Disembodiment: $t_{19}=24.5$, $z=2.84$, $p=0.005$). As predicted, we found a significant difference between conditions in the mean error, with more negative values, indexing greater attraction towards the alien hand, in the synchronous as compared to the asynchronous condition ($t_{19}=37$; $z=2.52$; $p=0.01$; see Fig. 12 panel A). Crucially, results showed a significant negative correlation between the error score and both the embodiment ($r_{18}=-0.49$; $p=0.03$; see Fig. Fig. 12 panel B) and the disembodiment ($r_{18}=-0.55$; $p=0.01$; see Fig. 12 panel C) scores, indicating that the magnitude of the attraction toward the rubber hand correlated with the degree of (dis)embodiment.

Finally, the proprioceptive drift analysis confirmed that the proprioceptive judgement was significantly more shifted towards the alien hand after the synchronous as compared to the asynchronous RHI (t_{13}=16, z=2.29, p=0.02).

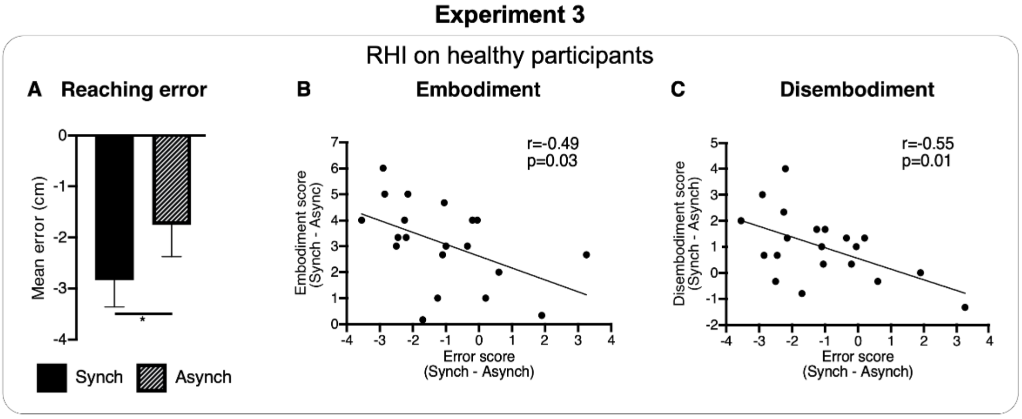

Fig. 12 Results of Experiment 3: RHI on healthy participants. The plot in A represents the mean error in the synchronous (solid) and asynchronous (striped) block. The plot in B and C represent the correlation between the error score (mean error in the synchronous – asynchronous block) and, respectively, the embodiment and the disembodiment scores (mean ratings in synchronous – asynchronous block). Error bars represent the standard error of the mean (SEM) and asterisks represent the significant differences (*p<0.025).

Discussion

In the present study, we adopted a neuropsychological approach to investigate the relationship between the sense of body ownership and reach planning, isolating the embodiment-effect from the confounds of spared proprioception. To tackle this issue, we took advantage of brain damaged patients affected by proprioceptive deafferentation, thus allowing us to rule out proprioception. More specifically, we had the opportunity of testing two rare cases of brain-damaged patients affected by pathological embodiment (E+1 and E+2), who still had complete motor function of the contralesional upper limb, and a well-matched control patient, who had the same neuropsychological profile except that he did not present pathological embodiment (E-). First, we contrasted the E+1 performance with that of the E- control case (Experiment 1). We asked these patients to perform simple reaches towards a target without visual feedback immediately after observing either an alien (embodied) hand or a fake (not embodied) hand (*memory guided reaching task*). The results highlight that, irrespective of proprioception, damaged in both patients, only the E+ patient, when he embodied the alien hand, made drastic errors that were consistent with the pathological belief that someone else's hand was his own. Then, we performed a second experiment (Experiment 2) wherein E+2 underwent the reaching task both with (*visually guided* task) and without (*memory guided* task) visual feedback of the target. The results confirmed those of Experiment 1, also revealing that the embodiment-dependent effect was present irrespective of the visual occlusion of the target.

Previous studies have capitalized on neuropsychological evidence to investigate the effect of the incorporation of an alien limb on the motor system, focusing on the movements of the alien - and not the patient's - hand. Conversely, in the present study we had the chance of testing E+ cases with spared motor function, allowing us to directly examine the effect of embodiment on *their own* hand's movements. By measuring the embodiment-effect in absence of proprioception in able-to-move E+ patients, we provide evidence that body ownership is a crucial variable employed in reach planning.

In the memory guided task, the mean error of the E+1 was significantly more shifted to the left compared to that of the E- patient, as if he planned movements from the position of the alien (embodied) hand. Note that, the evaluation of both E+ patients revealed that embodiment was present only for the alien, and not for the rubber hand. The absence of rubber hand embodiment confirms previous observations, suggesting that the categorization between biological and non-biological objects is preserved in E+ and that the deficit is present only when biological stimuli are involved (Candini et al., 2022). However, some reaching bias was observed also when the rubber (control) hand was presented. This result was confirmed also in E+2, in both memory and visually guided tasks, demonstrating that, in a patient affected by body ownership disturbance, when a hand-shaped object is placed in a body-congruent position, it is able to elicit a visual capture mechanism that attracts the starting point of the movement vector (i.e., the hand's perceived resting location). Previous interesting work by Martinaud and colleagues demonstrated that proprioceptive impairment correlates with the elicitation of a feeling of ownership towards a fake hand in right brain-damaged patients (Martinaud et al., 2017). The authors showed that simple visual exposure to the dummy limb (while the own hand is hidden from view) modulates body ownership, leading patients to report a feeling "as if" the fake limb was their own. This finding provides evidence that the hand-shape constraint plays an important role in limb ownership. Coherently, our data show that, although E+ patients do not ascribe the fake hand to the own body, some residual visual capture can be measured through a reaching task. However, only in E+1 and E+2 (and not in the E-) patients did we observe a crucial difference between the alien and the rubber hand block. In other words, it is noteworthy that in both experiments, including different patients and different tasks, only in those patients that were affected by pathological embodiment, the alien (embodied) hand caused a greater attraction of the movement vector as compared to the rubber (not embodied) hand, thus suggesting that this result cannot be ascribed only to a sort of "visual capture" induced by the hand-shaped object.

Moreover, in the context of the classical dissociation between the vision-for-perception (the so-called *what* or *ventral* stream) and the vision-for-action (the so-called *where*/*how* or *dorsal* stream) (Goodale & Milner, 1992; Ungerleider & Haxby, 1994), pathological embodiment has been described as a malfunction of the vision-for-perception mechanism (Errante et al., 2022; Garbarini et al., 2020; Pia et al., 2020). That is, an inability to discriminate the self-body from the others' bodies, which leads to the embodiment of the alien hand when appropriately positioned. The results of the present study suggest that pathological embodiment also entails a defective vision-for-action mechanism. Indeed, according to the two-visual-systems hypothesis (Goodale & Milner, 1992; Milner & Goodale, 2008), while memory-guided movements towards the remembered position of a hidden target requires contributions not only from the dorsal but also from the ventral stream, programming and control of visually-guided reaching rely on the dorsal stream only (Cornelsen et al., 2016; Goodale et al., 2004; Goodale & Westwood, 2004). Hence, while in Experiment 1 we could not dissociate the involvement of the dorsal stream from that of the ventral stream since a memory guided task was employed, Experiment 2, which leveraged a visually guided task, allowed us to isolate the involvement of the dorsal stream in pathological embodiment. The results revealed that, irrespective of the task, the E+2 patient showed a greater shift of the movement vector towards the alien hand, coherently with the pathological belief of owing that hand. This result suggests that the top-down modulation exerted by the sense of body ownership on motor control involves both memory guided and online movement planning and execution, affecting both their underlying networks.

Taken together, these findings suggest that E+ patients plan reaches from the spatial position of the *embodied* hand and not from the position of the *own* hand, in line with previous RHI studies. In this context, contrasting evidence comes from a neuropsychological study by Preston and colleagues, supporting a dissociation between embodiment and reaching drift (Preston et al., 2011). In this study, a brain-damaged patient affected by neglect performed reaches with the ipsilesional right hand, while observing two right moving hands, positioned 6 cm either to the left or the right of his hidden hand. Although in a previous study employing the very same paradigm, healthy participants tended to program movements from the hand which was nearer to the body midline and explicitly incorporated both hands (Newport et al., 2010), this patient demonstrated motor control only over the right hand of the pair and reported embodiment only of the hand positioned to the left. While the results of the reaching performance are consistent with his extrapersonal neglect, the report of embodiment over the left hand is surprising. To sum up, this single case study demonstrates that attentional factors modulate differently the mechanisms underlying embodiment and motor control. However, in our study, wherein both E+ and E- patients were matched for the presence of neglect, it seems that attentional factors cannot explain the results we found. Indeed, in our data, the movement endpoint was consistent with the starting position of the hand believed to be one's own, i.e., the own hand in the E- patient, the alien hand in both E+ patients.

To corroborate this neuropsychological evidence, in Experiment 3, we investigated the embodiment-effect on reaching in participants with intact proprioception undergoing the RHI.

We found that reaching errors were significantly shifted towards the left only when the illusion was experienced, highlighting that the embodiment of the alien hand significantly attracted the reaching movement's vector. This result confirms previous evidence (Fang et al., 2019; Holmes et al., 2006; Zopf, Truong, et al., 2011), also expanding it with an important new finding, i.e., the magnitude of the reaching error correlated with both the amount of illusory embodiment of the alien hand and the amount of illusory disembodiment of the physical limb. This demonstrates that the degree of reaching error depends on how much the alien hand is considered as the own.

In conclusion, we show that the delusional belief of owning the alien hand leads to remap the representation of the own hand location onto that of alien (embodied) hand, thus planning and executing movements from an erroneous starting position. In other words, we demonstrate that, when the proprioceptive confound is controlled, body ownership and motor control are intimately linked, with the former exerting a top-down influence on the latter. Our results suggest that, when planning a reach, we may do so from where the *owned* hand is and not from the location of the hand which is physically attached to the body.

Study 1.2: The Rubber Hand Illusion reveals modulation of body awareness in humans and monkey

[This research is in preparation for eLife as Errante, A., Rossi Sebastiano, A., Castellani, N., Rozzi, S., Fogassi, L., Garbarini, F. The Rubber Hand Illusion reveals modulation of body awareness in humans and monkey]

Introduction

The results of Study 1.1 allowed us to draw the conclusion that, when an alien hand is embodied, we plan hand movements as if they started from the alien hand position. This demonstrates how the nervous system plans movements performed with the affected/deceived hand. In Study 1.2, we started from the observation of the E+ patients behaviour during the evaluation. As previously described, if we ask E+ patients to move the unaffected hand to reach the affected one, they reach for the alien hand, because they recognize it as their own. This paradoxical behaviour happens only when the alien hand is in a body-congruent position, so internally aligned with the patient's shoulder, and not when it is in incompatible positions (Garbarini et al., 2020; Pia et al., 2020). Against this background, we aimed to complement the previously described study, by addressing how the nervous system plans movements toward the hand which is subject to a sort of disembodiment, as a result of an alien hand embodiment. In other words, we explored whether, following embodiment of an alien hand, self-directed movements aimed to the involved body part are performed taking into account the own or the alien hand as a target. We tackled this issue capitalizing on the classical visuo-tactile RHI. Crucially, to test whether this illusory embodiment is able to deceive the motor system of not only humans, but also the non-humans primates, we tested a monkey with the very same paradigm employed in the cohort of humans. In agreement with human studies, pioneering studies in non-human primates that exploited the RHI procedure, showed that bimodal (tactile and visual) neurons in PMv and posterior parietal area 5 not only respond to the felt position of the real arm when the arm is covered from view, but also to the seen position of a fake embodied arm (Graziano et al., 2000;1999). To sum up, "we know that the monkey’s neurons are fooled by the fake hand, but whether the fake hand is able to fool the monkey’s behaviour remains unclear” (Graziano, 1999).

The present experiment was conceived within the BAMBI project (the Body in human and Monkey BraIn). The general aim of the project was to study the emergence of the sense of body ownership in an ontogenetic and phylogenetic perspective. Here, we adopted a phylogenetic perspective and we investigated to what extent the non-human primate brain is flexible and ruled by the very same constraints regulating human primates’ body representations. To address these research questions, capitalizing on a modified version of the motor evaluation test used to assess pathological embodiment in brain-damaged patients, we investigated, in the cohort of humans and in the monkey, whether the embodiment of a fake hand modulates the kinematics of self-directed movements aimed towards the hand subjected to the RHI.

Materials and Methods

Participants

Monkey

The experiment was carried out on a male Rhesus monkey (Macaca Mulatta) weighing about 10 kg. All methods were performed in accordance with relevant guidelines and regulations. In particular, the animal handling, as well the behavioral procedures, complied with the European guidelines (2010/63/EU) and Italian laws in force on the care and use of laboratory animals, and were approved by the Veterinarian Animal Care and Use Committee of the University of Parma (IT) (Prot. 78/12 17/07/2012) and authorized by the Italian Healthy Ministry.

Human participants

Twenty-eight human volunteers (20 females; mean age ± standard deviation: 25.81 ± 7.12 years; range 20-59 years) also participated in the study. All subjects had normal or corrected-to- normal vision. Only subjects with no history of neurological, orthopedic or rheumatological diseases, and no drug or alcohol abuse were recruited. All participants were right-handed according to the Edinburgh Handedness Scale (R. Oldfield, 1971). Eight participants were subsequently excluded from data analysis due to technical problems during data acquisition. Overall, 20 participants were included in the successive analyses (15 females; mean age ± standard deviation: 26.42 ± 8.25 years; range 20-59 years). Informed consent was obtained in accordance with ethical standards set out by the Declaration of Helsinki (1964). The study was approved by ethical committee of the University of Turin (Prot. 133, 278 7/03/2019).

Experimental apparatus and materials

Monkey experiment

The monkey faced a horizontal table consisting in a box, located at the belly height (dimensions 50 × 60 × 50 cm). The lower part of the box consisted of a horizontal plane (42 × 50 × 1.5 cm) on which three metal cylinders (starting point) were positioned, at about 20 cm from the monkey body. The first was aligned with the right shoulder of the monkey, while the other two were placed on the left, one in a medial position, aligned with the monkey's left shoulder (*internal position*), and the other in a lateral position, misaligned with the monkey's left shoulder (*external position*), at about 5 cm from the previous one. The upper part of the box contained a transparent plexiglass frame (39 × 49 × 2 cm), at the shoulder level, tilted of about 8° in the antero-posterior axis, with the lowest part towards the monkey neck. This frame allowed to insert, depending on the condition, one opaque panel (39 × 10 × 1 cm), that could obscure either the internal position or the external one, making the left hand of the monkey covered from view (see below, experimental paradigm).

In both baseline and experimental conditions, a fake left arm, similar to the monkey one, was introduced. The fake arm was made of fiberglass and covered with synthetic leather produced by a taxidermic procedure. On the horizontal plane, in front of each left cylinder, a red LED was positioned. It was connected to a PC operating with LabVIEW 2010 environment (National Instrument; http://www.ni.com/labview).

Human experiment

The participants sat on a chair in front of a table, on which a wooden apparatus (32 × 100 × 65 cm), similar to that used in the monkey experiment, but adapted for human subjects, was placed. The apparatus had a removable horizontal opaque panel that could be placed on its upper part (occluding the participant left limb from vision). In the starting position, participants placed their hands inside the apparatus with the palm down. In this rest position they were required to hold their right and left index fingers on marked points. The starting point of the right hand was placed on the right side at 20 cm from the body midline. Instead, on the left side the hand could be placed in two possible points: one corresponding to the *internal position*, aligned with the subject's shoulder (20 cm from the body midline) and the other corresponding to the *external position*, misaligned with respect to the subject's shoulder (40 cm from the body midline). In both baseline and experimental conditions, a rubber dummy hand (fake hand), matching the participant's biological gender, was introduced. A red LED was positioned in front of the rubber hand.

Experimental procedures

Monkey training

At the beginning, the monkey was habituated to the interaction with the experimenters in its home cage, by receiving food and being touched. Then it was trained to leave the cage and to seat in a primate chair, and familiarize with the experimental setup. After this preliminary phase (lasting about 3 months), the monkey was trained to perform a specific reaching task. First, the monkey was trained to hold both hands on the starting points. Then, it was habituated to be touched by the experimenter on the left forearm or left cheek without moving and, later on, to respond to the touch by reaching the stimulated body part with the right hand. Subsequently, the conditioning stimulus (touch) was substituted with the visual cue (LED). Finally, the monkey fake limb was introduced at the left-hand position not occupied by the monkey's own hand and trained the monkey to fixate the fake hand, while an experimenter gently stroked with a brush both the monkey forelimb (from forearm to hand) and the fake one for about 2 minutes. This type of procedure was similar to the rubber hand illusion (RHI) procedure used in previous studies on humans (Matthew Botvinick & Cohen, 1998a) and monkeys (Graziano et al., 2000).

Each phase of habituation and training was achieved by using a positive reinforcement technique. Reinforcement consisted in palatable food and liquids.

Monkey and humans Rubber Hand Illusion procedure

Participants (monkey or humans) placed their hands in the apparatus on the starting points, i.e., with the right hand on the corresponding marked point, and the left hand either in the internal or in the external position. The fake hand was placed in the internal/external position (not occupied by the real hand) and the opaque panel was introduced, preventing the participant from seeing the left hand, but allowing the view of the fake hand. In the human experiment, a white cloth covered the shoulders and the proximal parts of the left real and dummy hand, so that the participant could not appreciate the discontinuity between the rubber hand and the body. In the monkey experiment, the opaque panel was enough to prevent the view of such discontinuity. Then, the experimenter stroked the participant's left hand and the fake hand either synchronously or asynchronously for 2 minutes. In the synchronous (illusion) conditions, the stroking was on the two hands was applied with the same timing. Conversely, in the asynchronous (control) conditions, the strokes on the real and fake hands were applied in anti-phase. This procedure was immediately followed by the reaching task (see below), wherein each movement was interleaved with 13-15 seconds of RHI stimulation.

In order to measure the effectiveness of the RHI procedures in the human experiment, explicit and implicit measures were analyzed.

Implicit measures. Before performing the RHI procedure, the entire apparatus was covered with a black panel and 10 proprioceptive judgements (proprioceptive judgement pre) about the perceived position of the left index finger were collected. To this aim, a ruler of (1 m) length was positioned horizontally over the apparatus, and participants were asked to judge the location of their index finger by verbally reporting the number on the ruler that corresponded to the felt location of their left index finger. In order to avoid that the participant could anchor judgement to a given number, for each trial of the proprioceptive judgement the ruler was placed on the black panel of the apparatus with its right limit at variable positions. The experimenter recorded not only the number reported by the participant, but also the number corresponding to the right limit of the box, and we considered the delta between the two numbers (i.e., the distance between the right angle of the box and the index position reported by the participant) as a proprioceptive judgement. Another set of 10 proprioceptive judgements was collected (proprioceptive judgements post) after each block of 15 trials of the reaching task.

Explicit measures. At the end of each block, participants were asked to rate their agreement with the items of the Embodiment questionnaire. Such questionnaire consisted of 3 “real” items, testing the feeling of embodiment, and 3 “control” items, controlling for response bias [(Longo et al., 2008); see Table 3].

1. It seemed as if I were sensing the touch in the location where I saw the rubber hand touched

2. It seemed as if the touch I felt was caused by the paintbrush touching the rubber hand

3. I felt as if the rubber hand was my hand

4. I felt as if my real hand was becoming a fake hand

5. I felt as if I had more than a left hand

6. I felt as if the rubber hand was shifting towards my left hand

Table 3. Embodiment questionnaire Participants were asked to rate their agreement with the statements by assigning a score to each item, using a 7 points Likert Scale (-3 = “strongly disagree”; +3 = “strongly agree”) (Longo et al., 2008). Note that the first three statements represent “real” items investigating the illusory feeling of ownership towards the fake hand, whereas the last three are “control” items, to control for response bias. Items were presented in a random order.

Reaching Task procedure

The experiment consisted of two baseline conditions and four experimental conditions (see Fig. 13): a) " Internal Baseline", the fake hand was placed in the internal position, and the reaching task was performed in the absence of any RHI stimulation; b) “External Baseline”, the fake hand was positioned in the external position, and the reaching task was performed in the absence of any RHI stimulation; c) “Internal Synchronous”, the position of the fake hand was internal and synchronous RHI stimulation was applied; d) “External Synchronous”, the position of the fake hand was external and synchronous RHI stimulation was applied; e) “Internal Asynchronous”, the position of the fake hand was internal and asynchronous RHI stimulation was applied; f) “External Asynchronous”, the position of the fake hand was external and the asynchronous RHI stimulation was applied.

Before each experimental condition, the experimenter applied the RHI stimulation (see *Rubber Hand Illusion procedure* above) for 2 minutes. In order to maintain the illusion throughout the task, the RHI stimulation was continuously applied for about 10-12 s, followed by a single trial of the reaching task.

Human participants were instructed to reach and touch their left hand with their right hand, starting from the right starting point, and the monkey was specifically trained for the task as outlined above (see *Monkey training*). The red LED was employed as a go signal for the movement. If the participant performed additional movements of the arm at any time during the initial holding period, the trial was aborted. Participants were not allowed to make any correction once the pointing hand had reached the target hand. Data in the monkey were acquired in 5 different days. For each day, 20 trials were collected for each of the baseline and experimental conditions. Thus, in the entire experiment, the monkey performed a total of 600 trials (20 trials x 6 conditions x 5 days). Conversely, data in human participants were acquired in a single session. For each participant, a total of 180 trials (30 trials x 6 conditions) were collected.

All the baseline and the experimental conditions were performed in separate blocks. The order of the baseline conditions, always performed at the beginning of the session, was counterbalanced between participants. In the monkey experiment, the order of the experimental conditions was counterbalanced across sessions: in half of the sessions the internal conditions were presented first, in the other half vice versa, alternating synchronous and asynchronous stimulation blocks. In the human experiment, the order of experimental conditions was randomized between participants. Each experimental condition was divided into 2 mini-blocks. Between the mini blocks, a set of proprioceptive judgements was collected. Between different blocks/conditions a five-minute pause was required, in order to change the setting and also to cancel the effects of the illusion, preventing possible interactions with successive trials.

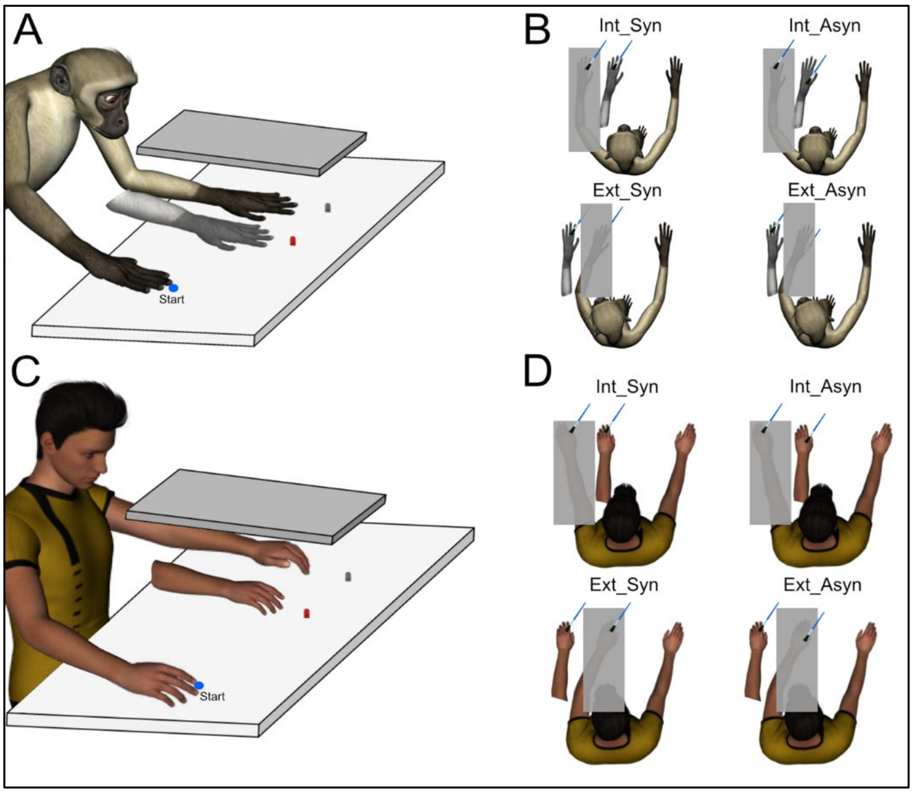

Fig. 13. Illustration of the experimental paradigm carried out on the monkey and humans. (A-B) Before each trial, the subject remained in a rest state, with the hands on the starting points. In (A) and (C), an example of the internal position is depicted: the fake hand (in gray) was placed in the internal position, aligned with the subject left shoulder, while the real left hand was hidden from the view of the subject, by means of an opaque panel. (B, D) The paradigm consisted of four experimental conditions (see Methods). In all conditions, the fake hand was visible, while the real left hand was always hidden from the subject view. In each condition, after 12 seconds of visuo-tactile RHI stimulation, a red LED was switched on, prompting the subject to perform the reaching movement with the right hand towards the left hand.

Data analysis

Kinematic data preprocessing

All performed reaching movements were videorecorded and analyzed using 2D kinematic analysis. Data were acquired by means of a digital HD camera (© GoPro, Inc., USA), with a 240 frame/s rate and resolution of 1280x720p. The experiment consisted of 100 repetitions of the same action for each condition in the monkey, and 30 repetitions in human participants. Note that, in the monkey data, twenty trials equally distributed between conditions were subsequently excluded from the analysis due either to technical problems, such as the lack of synchronization between camera and PC station, or to the motor anticipation of the go-signal by the monkey. Thus, the final dataset acquired in the monkey included a total of 480 trials and the final one acquired in humans included a total of 3600 trials (180 trials x 20 participants), distributed in six conditions.

The Tracker software (© Tracker v5.1.2, 2019 Douglas Brown) was used to measure the movement trajectory and velocity, by marking specific points placed on the subject's hand. In the experiment on humans the markers consisted of colored spheres (ø 0.5cm) placed on the tip of the participant's right index finger. In the monkey experiment, a light blue colored marker was painted centered on the knuckle of the right little finger. The size of this latter marker was about 3cm of diameter, thus larger with respect to the that used for humans, due the difficulty of automatically tracking a marker moving at high velocity (velocity peak about 360 cm/s in the monkey vs 130 cm/s in humans). Using this arrangement, it was possible to calculate trajectory on x and y axes, and max peak velocity. The point of origin of the X/Y axes was set as the starting position of the subject's hand. To trace the markers, the auto-tracker function implemented in Tracker software was used. This procedure compares the image of the marker in each frame with its template image. More specifically, we created a point of mass in the centre of the marker, using as tracking parameters an evolution rate of 20% and an auto-mark value of 4 (range 1-10). This setting reduces the probability of drifts in the template and false matches. Using these parameters, it was possible to trace marker position in the space every 4 ms until the end of the action. A line of 15 cm drawn on the side of the apparatus was used as reference measure for software calibration. The calibration was computed by scaling the real distance measured in cm to the image distance expressed in pixels. Trajectory and velocity calculated by using the coordinates of the point of mass on the x and y axis. Velocity index was calculated using a finite difference algorithm:

$$v = (x \cdot [i+1] - x \cdot [i-1]) / (2 * dt)$$

where i refers to the step number and dt is the time between two consecutive steps expressed in ms. The velocity module accounts both for the x and y components, by calculating the combination of the two vector values, expressed in cm/s. In order to account for the noise in the recorded data, values were averaged and smoothed by using a gaussian-weighted moving average filter included in Matlab R2020a (The Mathworks, Inc., Natick, MA, USA). In order to account for differences between trials having slightly different durations, we normalized each trial duration using the percentage of the total time and calculated and plotted mean velocity and trajectory data over movement time percentage.

Kinematic data analysis

In order to estimate the drift on x-displacement during the performance of the reaching task, we computed for each trial the difference between the final position on the marker during the Synchronous and Asynchronous conditions (both Internal and External) and the respective Baseline (Internal, External). Note that positive and negative values were normalized so that both in the case of the Internal and the External conditions, positive values of the drift indicate always a shift towards the fake hand, while negative values indicate a drift towards the real hand. The data on displacement drifts were analyzed using two different repeated-measures ANOVAs, one for the monkey data and the other for the human data. The magnitude of the drift was entered in each ANOVA as a dependent variable in a 2×2 repeated-measures ANOVA, with *Position* (Internal, External) and *Stimulation* (Synchronous, Asynchronous) as repeated measures. Post-hoc comparisons were carried out by means of Newman-Keuls' test.

Velocity peaks were analyzed using two different repeated-measures ANOVAs, one for the monkey data and one for the human data. Hence, each one of these velocity parameters were entered as a dependent variable in a 2×3 repeated-measures ANOVA, with *Position* (Internal, External) and *Stimulation* (Synchronous, Asynchronous, Baseline) as repeated measures. Post-hoc comparisons were carried out by means of Newman-Keuls' test.

Explicit and implicit RHI measures analysis

To compare the subjective feeling of embodiment toward the fake hand across conditions, an Embodiment score was computed as the delta between the mean ratings attributed to the real and the control items of the Embodiment questionnaire (Embodiment score = real – control) and entered as a dependent variable in a 2×2 repeated-measures ANOVA, with Position (Internal, External) and Stimulation (Synchronous, Asynchronous) as factors. High Embodiment scores indicated strong feeling of embodiment. Furthermore, as an implicit measure of the RHI effect, we calculated the proprioceptive drift, namely the shift of the felt position of the participant's right hand towards the rubber hand (Tsakiris & Haggard, 2005). We averaged each set of proprioceptive judgements (separately for each experimental condition), and we subtracted the mean of the proprioceptive judgments pre- to the mean of the proprioceptive judgments post-, obtaining a measure of the proprioceptive drift in all experimental conditions. High values of proprioceptive drift indicated a great shift towards the rubber hand (i.e., a stronger RHI effect). Proprioceptive drift values were entered in a 2×2 repeated-measures ANOVA, with Position (Internal, External) and Stimulation (Synchronous, Asynchronous) as factors. For both explicit and implicit RHI analyses, post-hoc comparisons were carried out by means of Newman-Keuls' test.

Before running parametric tests, normality of the residuals was checked by means of the Shapiro Wilk test (p always>0.05). Statistical analyses were performed using Statistica Software (StatSoft, release 8).

Results

Kinematic data

Fig. 14 represents the full trajectories in each condition (i.e., the average among trials in each condition for the monkey – panels above – and the grand average of the 20 human subjects – panels below).

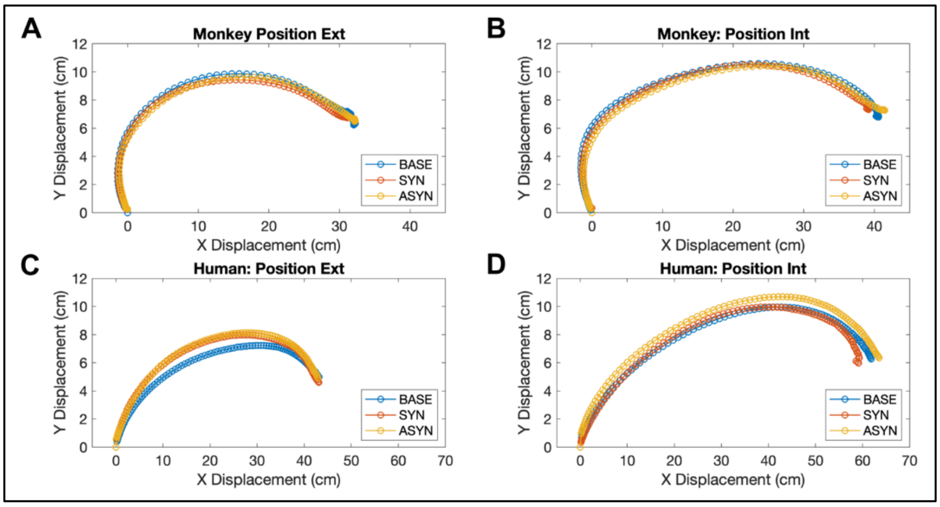

Fig. 14. Mean x and y displacement (trajectory) for the four experimental conditions and the two baseline conditions, in both humans and monkey.

We firstly analyzed the final position of the trajectory on the x-axis and calculated a drift measure, computed as the difference between the final position in each condition and the mean end-point in the corresponding baseline. Fig. 15 represents the magnitude and direction of the drift measure in both the monkey and humans.

Concerning the monkey, the 2×2 ANOVA (*Position*: Internal/External; *Stimulation:* Synchronous/Asynchronous) showed a significant *Position x Stimulation* interaction [$F_{(1,79)}$=8.85, *p*=0.003], with a grater drift towards the fake hand in the Synchronous stimulation as compared to the Asynchronous one, in the Internal position (*p*=0.01) (Fig. 15 panel B). Note that, the drift in Synchronous Internal condition was significantly greater than that in the Synchronous External (*p*=0.0003) and Asynchronous External (*p*=0.019) conditions as well. An opposite drift, although not significant (*p*=0.11), was also present following Synchronous vs Asynchronous stimulation, when the fake arm was placed in the External position (Fig. 15 panel A).

Concerning the human participants, the 2×2 ANOVA revealed a significant *Position x Stimulation* interaction [$F_{(1,19)}$=4.55, *p*=0.03], similar to that observed in monkey. When the fake arm was in the Internal position and the stimulation was Synchronous, the final position of the movement was significantly more shifted toward the fake arm, as compared to the Asynchronous stimulation

(p=0.015) (Fig. 15 panel D). Similar to the monkey experiment, the drift in the Synchronous Internal condition was significantly greater than that in Synchronous External (p=0.026) and Asynchronous External (p=0.042) conditions. No significant difference in the drift measure was present between Synchronous and Asynchronous stimulation, when the fake arm was placed in the External position (p=0.83) (Fig. 15 panel C).

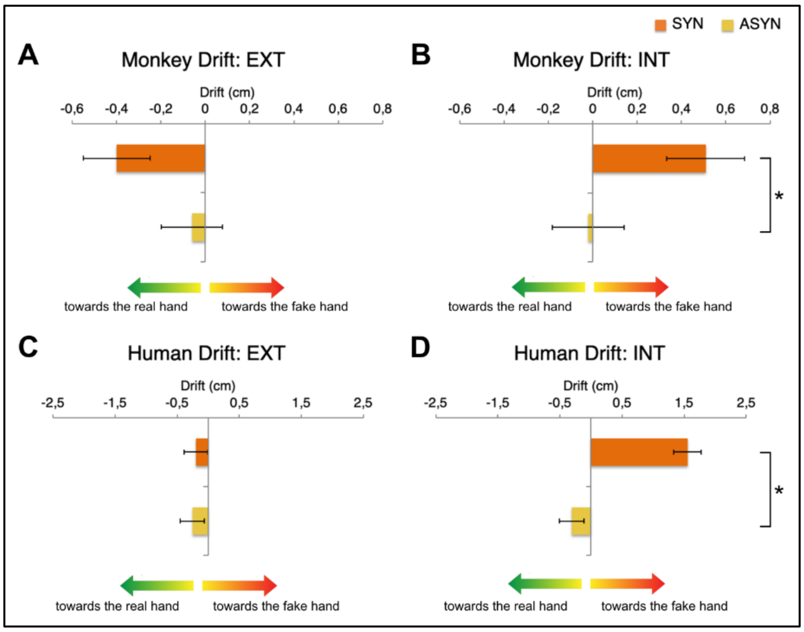

Fig. 15. Mean maximum drift in x displacement calculated for reaching movements performed by the monkey (A, B) and human participants (C, D). Error bars represent standard error mean. Asterisks indicate significant results.

The second analysis focused on maximum velocity peak. Velocity profiles, calculated separately for monkey and humans, are presented in Fig. 16.

In the monkey, the 2×3 ANOVA (*Position*: Internal/External; *Stimulation:* Synchronous/Asynchronous/Baseline) carried out on data about maximum velocity peak showed significant main effects of *Position* [$F_{(1,79)}$=169.6, p<0.001] and *Stimulation* [$F(2,158)$=8.7, p<0.001] and, crucially, a significant *Position x Stimulation* interaction [$F_{(2,158)}$=6.5, p<0.001], indicating lower peaks in both the Internal Synchronous (p=0.00002) and Asynchronous (p=0.001) conditions as compared to Internal Baseline. Note that Synchronous and Asynchronous conditions also differed from each other in both Internal (*p*=0.017) and External (*p*=0.044) positions.

Concerning human participants, the 2×3 ANOVA carried out on maximum velocity peak revealed exclusively a main effect of *Position* [$F_{(1,19)}$=27.3, *p*<0.001], indicating higher velocity peaks when the fake arm was in the Internal position.

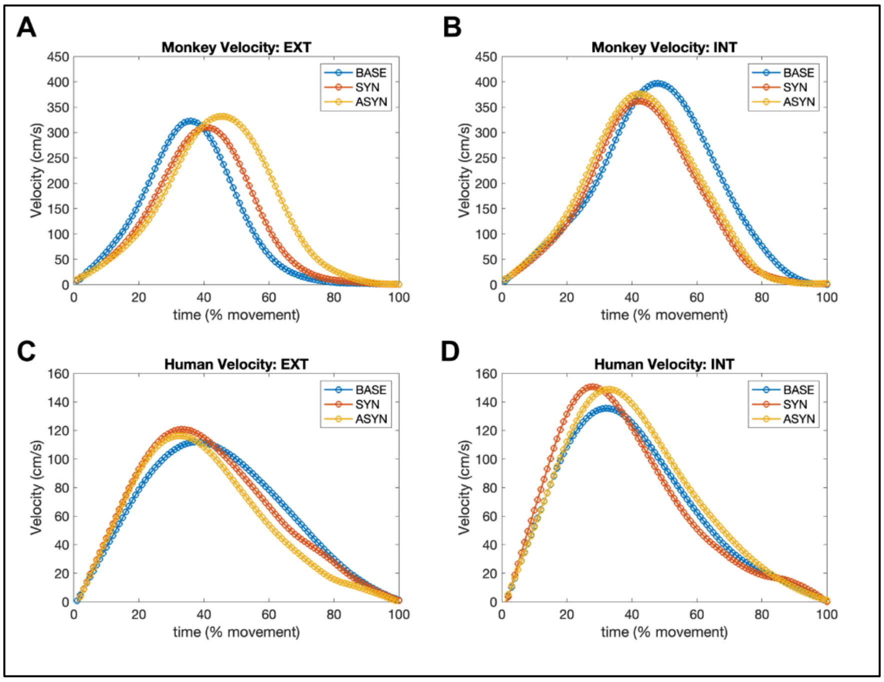

Fig. 16. Mean velocity profiles of reaching movements performed by the monkey (A, B) and human participants (C, D).

Explicit and implicit RHI measures

The 2×2 ANOVA (*Position*: Internal/External; *Stimulation*: Synchronous/Asynchronous) performed on the embodiment index revealed not only a significant main effect of both *Position* ($F_{(1,19)}$=4.38; *p*=0.04) and *Stimulation* ($F_{(1,19)}$=7.3; *p*=0.01), but, crucially, also a significant *Position* x *Stimulation* interaction ($F_{(1,19)}$=5.53; *p*=0.03; see Fig. 17 panel A). Newman-Keuls post-hoc tests showed that the difference between embodiment and control items was significantly greater in the Internal Synchronous condition, as compared to Internal Asynchronous (*p*=0.001), External Synchronous (*p*=0.002) and External Asynchronous (*p*=0.001). This confirmed that a greater feeling of embodiment over the fake hand took place only in the Internal Synchronous condition.

Regarding implicit RHI effectiveness measures, the 2×2 ANOVA (*Position*: Internal/External; *Stimulation:* Synchronous/Asynchronous) performed on proprioceptive drift values revealed not only a significant main effect of *Stimulation* ($F_{(1,19}=14.61$; $p=0.001$), but, interestingly, also a significant *Position* x *Stimulation* interaction ($F_{(1,19}=4.58$; $p=0.04$; see Fig. 17 panel B). Post-hoc analyses revealed that proprioceptive drift was significantly greater in the Internal Synchronous condition, as compared to Internal Asynchronous ($p=0.007$), External Synchronous ($p=0.013$) and External Asynchronous ($p=0.007$).

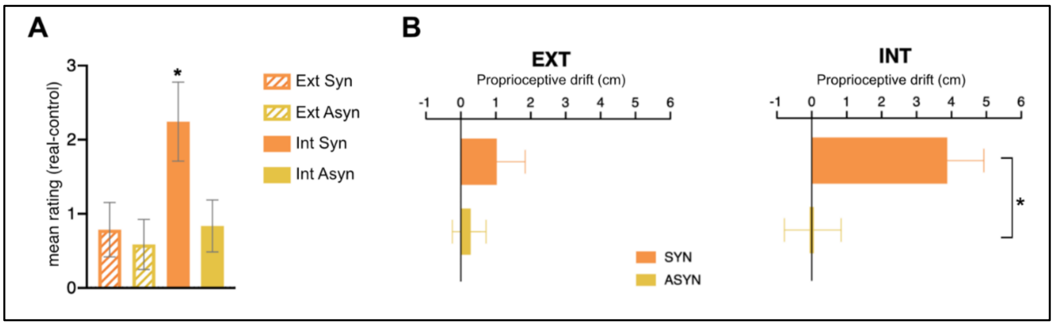

Fig. 17 **(A)** Embodiment index (calculated as mean rating in real – control items of the Embodiment questionnaire) in the four experimental conditions. **(B)** Proprioceptive drift (cm) for the four experimental conditions. Asterisks indicates significant results. Error bars represent the standard error of the mean (SEM).

Discussion

In Study 1.2, we addressed whether, when performing a self-directed movement, we aim towards the physical position of our body or to the position of the body which is believed to be our own. Crucially, in this study we aimed to verify whether similar mechanisms are present in humans and non-human primates, by testing a monkey with the very same protocol, running cross-species comparisons. Thus, the monkey and the group of humans were subjected to the rubber hand illusion on their left hand, in four conditions. In the first, synchronous internal condition, the rubber hand was placed aligned to the shoulder, in a body congruent condition and the tactile stroking was synchronous between hands. In this condition embodiment is normally elicited. Conversely in the other three conditions, embodiment should not occur either because the touch between hands was asynchronous, or because the fake limb war placed externally relative to the real hand, in a body-incongruent position. Our implicit and explicit RHI measures collected in the sample of human participants confirmed that embodiment occurred only in the internal synchronous condition, showing, in this condition, higher attraction of the hand felt position towards the rubber hand (i.e., proprioceptive drift) and higher ratings of perceived embodiment in the real as compared to control questionnaire items (i.e., embodiment index).

We tracked the participants and the monkey's movements towards their left (deceived) hand and off-line analysed a series of parameters, including the shift of the end-point of the movement in the RHI conditions with respect to the baseline and peak velocities.

Peak velocities showed different results in the monkey and in the human data. In humans, only between-positions differences emerged, confirming that velocity increased when larger movements were performed. In the monkey, differences between synchronous and asynchronous stimulation emerged in both positions, suggesting that they were related to the timing of the visuo-tactile stimulation, rather than embodiment per-se.

Conversely, the analyses on end-point shift led to more interesting, embodiment-related results. In the human group results, we found a significantly greater shift towards the fake hand in the synchronous than the asynchronous RHI condition, in the internal position. This result is in line with the results of the proprioceptive drift, showing that the perceived hand position was attracted only in the synchronous internal condition. Our data indicate that the trajectory of the movement was attracted towards the fake hand, when participants believed that this hand belonged to their own body and remapped the own hand position onto that of the embodied hand.

The monkey exhibited the very same pattern in the internal position, showing that also non-human primates are deluded by the RHI in a similar way to humans. This finding is in line with a previous study by Fang and collaborators that measured kinematics modulations following a different visuomotor illusion, able to elicit a visual capture of proprioception (Fang et al., 2019). Furthermore, it has been demonstrated that following a period of illusion induction, the monkey neurons in the primary somatosensory and motor cortices start responding also when tactile stimuli are applied only to the fake hand alone (Shokur et al., 2013). Note that, both studies focused on the behavioural or neural responses regarding the hand subjected to the illusion. Our findings originally show that the monkey is deluded by the classical visuo-tactile RHI so that its motor system target the fake limb when aiming to the deceived hand with the non-deceived one. Having determined that non-human primates share with human ones the flexible nature of the own body representation and that, in order for the illusion to occur, similar body schema constraints must be respected, future studies should disentangle the specific contribution of body schema constraints and visual recognition mechanisms in regulating bodily-self representations in monkeys. As planned in the BAMBI project, the monkey will undergo the very same task employed here while seeing both the fake and the real hand, after being deprived of proprioceptive input. In this way, we will investigate whether the monkey relies either on self-related visual details or on the congruency of the seen hands position with body schema constraint to drive the ownership judgement.

Altogether, these results bring out compelling evidence that both in human and non-human primates, the illusory belief of owning an alien limb, results in a remapping of the own hand location towards that of the alien hand, thus planning and executing movements towards the alien hand when aiming at the own hand. These findings are in line with the counterintuitive behaviour showed by brain-damaged patients affected by pathological embodiment who reach for the alien (embodied) hand instead of their controlesional one, whenever they are instructed to touch the own hand. In conclusion, when a self-directed movement is planned, both human and non-human primates aim to *the position where they believe our body-part is*, and not to its *physical position*.

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Chapter 3

The relationship between the sense of body ownership and sensory perception

The sense of touch is strongly related to the bodily self. The organ through which touch is conveyed, the skin, forms the first physical boundary between one's own body and the external world (Haan & Dijkerman, 2020). Moreover, the only object in the world on which we can perceive touch, is the own body. Hence, touch is a sensory system which is inherently linked to the ownership of our body parts. Neuropsychological evidence on pathological embodiment has suggested that a delusional incorporation of another person's body part may be sufficient to perceive tactile sensations on it. In a series of behavioral studies, we demonstrated that the alien (embodied) hand is functionally treated by the neural system as the patient's own limb, in both motor (Fossataro et al., 2016; Garbarini et al., 2015; Rossi Sebastiano, Romeo, et al., 2022) and sensory (Fossataro, Bruno, Gindri, Pia, et al., 2018; Garbarini et al., 2014) domains. Regarding the sensory domain, whenever these patients observe the alien hand being touched ('visual touch'), they tend to report tactile sensations on it, even though their physical body is not actually stimulated (Garbarini et al., 2014; Pia et al., 2013). Thus, such neuropsychological studies reveal that the brain is able to build tactile awareness merely upon the belief of owning a body. In other words, it suggests that we may perceive sensations on the body parts that we believe to be our own, which may or may not necessarily coincide with our physical limbs.

How does this phenomenon take place? A way to investigate this issue is to exploit the RHI. Indeed, when the illusion is elicited, participants report to feel as if the rubber hand were touched. They remap the tactile sensation from the own physical limb, to the alien one that is embodied, showing a body-ownership dependent modulation of tactile perception.

To better understand how this sensory perception shift is created during the RHI, we ran a series of studies (Study 2.1, Study 2.2 and Study 2.3), which were all inspired by the Predictive Coding Framework interpretation of the RHI (Apps & Tsakiris, 2014; Limanowski & Blankenburg, 2013). In this theoretical framework, the nervous system is an inference machine that gives explanations to sensations by constructing probabilistic models and then comparing them to the sensory information to update beliefs about its causes (Karl Friston & Kiebel, 2009). It does so in order to reduce the level of "surprise" associated with sensory events, to live in a highly predictable world (Karl Friston, 2010). Hence, when afferent inputs do not meet the previously consolidated probabilistic model, our brain either balances the weight attributed to the afferent sensory inputs in order to minimize the free energy (i.e., the un-explained) and confirm the probabilistic model, or it adjusts the new acquired information within the probabilistic model, in order for it to be more predictive in the future. According to this interpretation, during the synchronous stroking of both the participant's (hidden) hand and the fake (visible) one (i.e., synchronous RHI procedure), the afferent inputs coming from somatosensory (i.e., my hand is being touched) and visual (i.e., the fake hand is being touched) systems are conflicting under the probabilistic model that *"my body is the only object in the world on whose surface I feel touch when I see its surface being touched"*. This multisensory conflict likely generates an error signal (i.e., prediction error), which is resolved by the brain to restore a coherent representation of one's own body. It has been proposed that the neural mechanism through which the nervous system settles the conflict relies on the contribution of two simultaneous processes: on one hand the weight attributed to somatosensory input is downregulated, on the other hand the weight attributed to visual inputs is increased (Limanowski & Blankenburg, 2013; Zeller et al., 2016). The effect of this re-weighting is that the tactile sensation (i.e., *"I feel touch"*) is remapped onto the visual (i.e., *"I see touch on the rubber hand"*) input, so that the participant believes that touches originate from the fake hand, and thus, that the fake hand is the own hand (i.e., *"I feel touch while seeing the rubber hand being touched because the rubber hand belongs to my body"*).

In line with this hypothesis, pioneering neuroimaging works have highlighted a greater activation of parieto-premotor multisensory cortices during the illusion, suggesting that high-order cortices may be responsible for the settlement of such visuo-tactile conflict (Brozzoli et al., 2012; Casula et al., 2022; Ehrsson et al., 2004, 2005; Gentile et al., 2015; Golaszewski et al., 2021; Limanowski

& Blankenburg, 2015; Petkova et al., 2011). However, if this theory is correct, one should be able to measure not only an activation of high-order cortices, but also a detriment of somatosensory processing on the real hand and an enhancement of visual processing around the alien hand, both at the behavioural and at the electrophysiological level.

Although previous studies identified a prominent role of multisensory cortices as the neural signature of the illusory feeling of embodiment, the involvement primary sensory areas is still controversial. As concerns somatosensory cortices, behavioural evidence suggests an increase of tactile detection threshold, indexing attenuated somatosensory processing, after the illusion induction (Folegatti et al., 2009; Zopf, Harris, et al., 2011). Coherently, recent neurophysiological studies, suggest that the somatosensory cortex activity may be down-regulated (Hornburger et al., 2019; Isayama et al., 2019; Limanowski & Blankenburg, 2016; Sakamoto & Ifuku, 2021; D. Zeller et al., 2015; Daniel Zeller et al., 2016). By contrast, the role of the visual system has been less investigated, and whether multisensory areas upregulate or downregulate it to explain away the conflicting visual input coming from the rubber hand is still an open question.

In Study 2.1 (Rossi Sebastiano et al., 2021), we employed the psychophysical measure of perceptual threshold to measure a behavioural correlate of the somatosensory and visual modulations, to better understand the mechanisms underpinning the illusion. Before and after the RHI, participants underwent a tactile (Experiment 1) and a visual (Experiment 2) task, wherein they had to detect stimuli slightly above the perceptual threshold, and accuracy was taken as a behavioural measure of sensory perception.

In study 2.2 (Rossi Sebastiano et al., *in preparation*), we sought to verify this model at the neural level, by recording somatosensory-evoked potentials (SEPs) and visual-evoked potentials (VEPs) following the RHI induction. Event-related potentials to simple somatosensory and visual stimuli, (i.e., electrical stimulation of the median nerve and red LEDs appearing close to the rubber hand) were recorded following a period of RHI induction.

Having determined how the brain balances the afferent inputs in the somatosensory and visual domains, in study 2.3 (Pisoni et al., *in preparation*) we combined TMS and EEG following more ecological stimulations to investigate the neural mechanisms underpinning the remapping of the somatosensory content onto the visual input that takes place during the RHI. We analysed the S1 alpha-band connectivity changes across different conditions, i.e., the observation of touches occurring onto the rubber incorporated hand or real touches applied to the participant's hidden hand. With this methodology, we aimed to highlight the brain mechanisms through which we are able to feel a tactile sensation when touches are applied to an alien (embodied) hand, instead of our own, to uncover the inner potentiality of the healthy brain to build tactile awareness merely upon the belief of owning a body.

Study 2.1: Diametrical modulation of tactile and visual perceptual thresholds during the rubber hand illusion: a predictive coding account

[This research has been published in Rossi Sebastiano, A., Bruno, V., Ronga, I., Fossataro, I, Galigani, M., Neppi-Modona, M., Garbarini, F. (2021). Diametrical modulation of tactile and visual perceptual thresholds during the rubber hand illusion: a predictive coding account. Psychological Research. 10.1007/s00426-021-01608-0]

Introduction

As mentioned above, within the framework of the predictive coding theory (Friston, 2005), conflicts emerge when predictions, based on internal models explaining sensory events, do not meet the sensory feedback, generating a prediction error. In the synchronous condition of the RHI, the participant receives tactile (i.e., touches occurring onto the participant's hand) and visual (i.e., touches occurring onto the fake hand) touches, occurring at the same time and spatial location on the two hands. Given its attitude to resist entropy, our brain may try to solve the prediction error that is created in this condition, by modulating lower-level sensory processing by feedback projections, resulting in the elicitation of the bodily illusion (Apps & Tsakiris, 2014; K. J. Friston, 2005). Within this framework, the asynchronous (control) condition should not generate prediction errors, because tactile and visual stimuli are segregated in time and spatial location. Since the scenario of being touched and, in a separate moment, observing touch onto an external object is not in contrast with common sensory experience, it should be correctly predicted by internal models, thus not eliciting prediction errors' signals (see also Chapter 1).

Based on dynamic causal modelling of electrophysiological (EEG) data and Bayesian model comparison, Zeller and colleagues (Zeller, Friston, & Classen, 2016) proposed that, during the RHI, the conflicting somatosensory input is downregulated, while greater precision is afforded to visual input. According to their interpretation, to reduce the prediction error signal emerging from feeling the touch on one’s own hand and seeing the fake hand being stroked, the premotor cortex is likely to downregulate proprioceptive and tactile inputs and to allocate greater weight to visual input. Such modulation of bottom-up influence of tactile and visual input onto the multisensory node should be the basis of the illusory feeling of ownership. In this view, the downregulation of the somatosensory system during the RHI should result in worsened detection of tactile stimuli delivered over the real hand. In contrast, the increase of visual regions activity should result in improved detection of visual targets delivered near the fake hand.

In Experiment 1, we investigated the influence of the RHI in modulating the detection of near-threshold tactile stimulations delivered on the real hand. A tactile detection task in which unilateral and bilateral tactile stimuli were delivered to the participants’ hands was repeated twice, i.e., before and after the RHI (see Fig. 17, upper panel). We predicted to replicate previous evidence of decreased tactile detection during unilateral stimulations (Zopf, Harris, et al., 2011), also extending it to the bilateral stimulations. More precisely, if the alteration of body ownership relies on the increase of the somatosensory threshold, we expected to find a decreased detection of tactile stimuli delivered over the participants’ hand exposed to the illusion, in both unilateral and bilateral trials.

In a separate experiment (Experiment 2), we investigated the influence of the RHI in modulating the detection of near-threshold visual stimuli delivered around the fake hand. A visual detection task in which visual stimuli were displayed near the fake hand was repeated before and after the RHI (see Fig. 17, lower panel). If somatosensory and visual systems are modulated in opposite directions to solve the multisensory conflict originated by the RHI as proposed by Zeller and colleagues (Zeller et al., 2016), we expected to observe an increased detection of visual stimuli delivered around the rubber hand.

Materials and Methods

Participants

The sample size of each experiment was estimated with an a priori analysis employing G*Power software (www.psycho.uniduesseldorf.de/abteilungen/aap/gpower3) based on two different datasets in which tactile (Fossataro et al., *in preparation*) and visual (Ronga et al., 2018) detection modulations induced by prismatic adaptation trainings were measured in a between-subjects design where two groups performing real and sham prismatic adaptations were compared. The common effect of interest between these experiments and the present study is the modulation of detection accuracy following an experimental manipulation (i.e., prismatic adaptation there, RHI here). Hence, the effect size (dz) was calculated on detection results before and after prismatic adaptation, as in Ronga et al. (2018). A sample of 18 participants was estimated by the analysis on tactile detection data (α=.05; power (1-β)=.9; dz=0.82), whereas a sample of 15 participants was estimated by the analysis on the visual ones (α=.05; power (1-β)=.9; dz=0.92). Thus, to keep the sample size equal, we included 18 participants in both Experiment 1 [12 women; aged (mean ± SD): 23.94 ± 0.99 years; mean years of education ± SD: 16.89 ± 4] and Experiment 2 [14 women; aged 23.72 ± 1.27 years; mean years of education ± SD: 16.33 ± 0.77), consistently with previous studies employing the RHI (Burin et al., 2017; Fossataro et al., 2018). All participants were right handed according to the Edinburgh Handedness Inventory (R. C. Oldfield, 1971), had normal tactile sensitivity and normal (or corrected-to-normal) visual acuity. The two samples of participants were not different in terms of sex (U=144, p=.71), age (t_{34}=0.58, p=.56), or years of education (t_{34}=1.14, p=.26). They all gave informed consent to participate in the study, which was approved by the Ethical Committee of the University of Turin (prot. n°122571).

Experiment 1

Experimental procedure and timeline

In Experiment 1, we investigated the modulations of the tactile sensory threshold following the RHI. To this aim, participants underwent 2 minutes of RHI in order to induce the illusory experience, immediately followed by a detection task of tactile stimuli, in which the administration of each stimulus was preceded by 13-15 seconds of RHI visuo-tactile stimulation.

The 13-15 seconds of visuo-tactile stimulation were inserted in order to maintain the illusion throughout the task (della Gatta et al., 2016; Rossi Sebastiano, Poles, et al., 2022).

Participants underwent two sessions on different days, with at least a one-week break in between. The sessions were identical except for the RHI procedure, which could be either synchronous (i.e., Synchronous condition) or asynchronous (i.e., Asynchronous control condition). The sessions' order was counterbalanced among subjects, so that half of the participants performed the Synchronous condition in the first session and the Asynchronous condition in the second session, and vice-versa for the other half. The counterbalancing order was randomly assigned to subjects. Participants were comfortably seated with both hands lying on a desk. Their right hand was placed in the right compartment of a wooden box and a black piece of tissue covered the shoulders and the proximal parts of the arms (see *Rubber Hand Illusion*). After having determined the bilateral tactile threshold to set stimulation intensity (see *Electrical Stimulation*), a tactile detection task was performed (TD Pre) in order to define a baseline. Then, a measure of the right hand's felt position (see below) was collected (Proprioceptive Judgement Pre) and the RHI procedure started with 2 minutes of synchronous or asynchronous stimulation, according to the session. After the 2 minutes stimulation, known to induce the illusory experience only in the Synchronous condition, we administered the experimental procedure combining 13-15 seconds of (synchronous or asynchronous) RHI stimulation with one trial of tactile detection (TD Post). This procedure was repeated for 45 trials. At the end of the procedure, RHI classical measures (Proprioceptive Judgement Post and subjective ratings to the Embodiment and Disembodiment questionnaires, see Table 4) were collected (see Fig. 17).

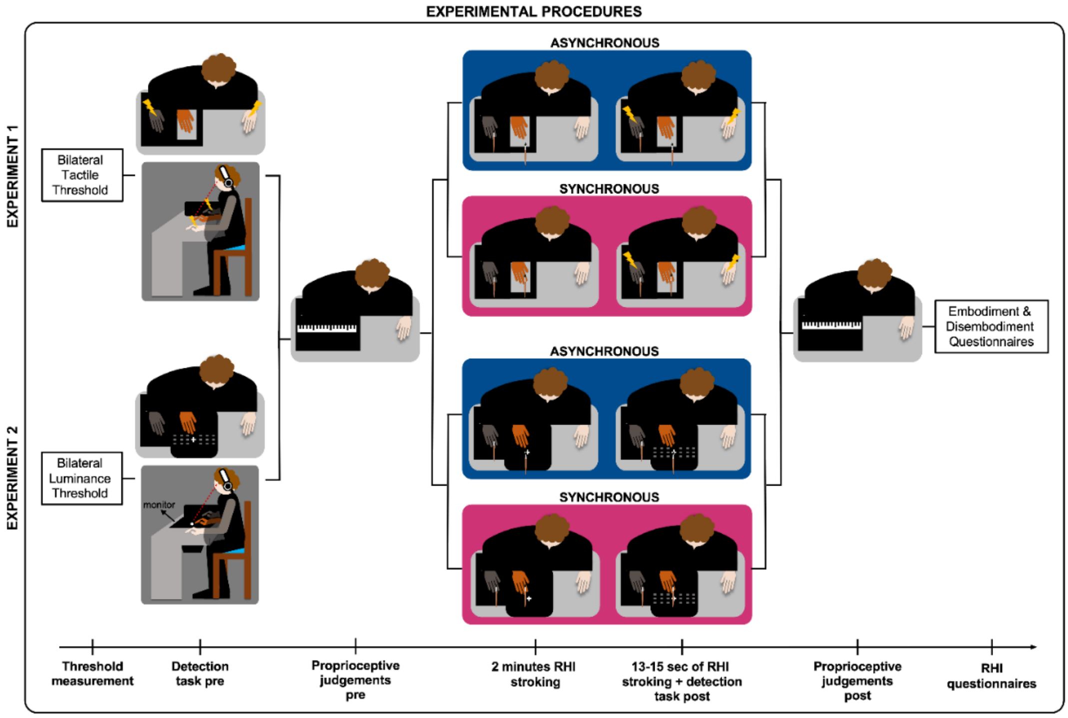

Fig. 17 Experimental Procedure of Experiment 1 & 2 After the bilateral threshold was estimated, participants underwent a *detection task pre* (Experiment 1: TD Pre; Experiment 2: VD Pre), wherein stimuli were administered with a jittering inter-trial-interval (13-15 seconds). Then, after five proprioceptive judgements about the right-hand index finger position were given by the subject, the 2 minutes (synchronous or asynchronous) RHI procedure was performed. Participants then underwent the *detection task post* (Experiment 1: TD Post; Experiment 2: VD Post), which was identical to the detection task pre, except that 13-15 seconds of RHI stimulation preceded each trial. Subsequently, five more proprioceptive judgements were performed by the participants. Finally, Embodiment and Disembodiment Questionnaires were administered. Note that, in Experiment 1 tactile stimuli were delivered on the participant's hands (20 bilateral, 10 on the right hand, 10 on the left hand, plus 5 catch trials), whereas in Experiment 2 visual stimuli could appear in 9 possible positions around the rubber hand (27 bilateral, 27 on the right side and 27 on the left side of the monitor, plus 5 catch trials).

Rubber Hand Illusion

The experimental materials used for the RHI procedure in Experiment 1 had already been employed in previous experiments (Bucchioni et al., 2016; Burin et al., 2017; Fossataro et al., 2018) and comprised a black wooden box (60 cm × 40 cm × 20 cm), a black piece of tissue and two realistic rubber hands (male and female). The box was divided into two compartments: the right one was covered by a black panel, while the top of the left compartment was open. At the beginning of the session, participants placed their right hand into the corresponding compartment so as to hide it from view, while the fake hand (male or female, according to the subject's biological gender) was positioned inside the left open compartment to make the fake hand visible. The participant's left hand was aligned with the left shoulder and the fake hand was aligned with the right shoulder, whereas the participant's right hand was externally positioned, 20 cm to the right of the fake hand. We took care that the fake hand was placed in an anatomically congruent position from the participant's egocentric perspective and that the black piece of tissue covered the shoulders and the proximal portions of the real and the dummy hand.

Before performing the RHI procedure, we covered the box with a wooden panel and collected five proprioceptive judgements (Proprioceptive Judgement Pre) about the perceived position of the right index finger. A ruler was positioned over the box, at the same gaze level of the fake hand, and participants were asked to judge the location of their index finger by verbally reporting the number on the ruler which corresponded to the felt location of their right index finger. For each proprioceptive judgement, the ruler was positioned on the box so that the number corresponding to its left limit was always different, in order that the participant could not anchor the judgement on a given number. The experimenter took note not only of the number reported by the participant, but also of the number corresponding to the left limit of the box, and we considered the delta between the two numbers (i.e., the distance between the left angle of the box and the index position reported by the participant) as a proprioceptive judgement. Afterwards, the wooden panel was removed, and the participant's right hand and the dummy hand were continuously stroked for 2 minutes by the experimenter. In the Synchronous condition, wherein RHI generally occurs, the stroking was synchronous in its timing and spatial location on the two hands. Conversely, in the Asynchronous condition, wherein RHI generally does not occur (i.e., control condition), the stroking was delayed and was therefore asynchronous in its timing and spatial location between the two hands.

The 2 minutes RHI procedure was immediately followed by the tactile detection task (TD Post, see *Tactile Detection task*), wherein each tactile stimulus was preceded by 13-15 seconds of RHI visuo-tactile stimulation. At the end of the tactile detection task, to measure the effectiveness of such procedure in inducing the illusion, we covered the box again and five more proprioceptive judgements were collected (Proprioceptive Judgement Post). In conclusion, participants were asked to rate their subjective feeling of ownership over the fake hand by answering to three items of the Embodiment Questionnaire (Botvinick & Cohen, 1998; Fossataro et al., 2018, see Table 4) and to rate their subjective feeling of disownership over their real hand by answering to three items of the Disembodiment Questionnaire (Longo et al., 2008; Fossataro et al., 2018, see Table 4). Participants were asked to rate their agreement with these items on a 7 points Likert Scale, ranging from "-3" ("strongly disagree") to "+3" ("strongly agree").

TABLE 4 Embodiment and Disembodiment Questionnaires (Fossataro et al., 2018; Longo et al., 2008) Participants were asked to rate their agreement with the following statements by assigning a score to each item, using a 7 points Likert Scale (-3 = "strongly disagree"; +3 = "strongly agree").

Embodiment Questionnaire	**1.** It seemed as if I were sensing the touch in the location where I saw the rubber hand touched
	2. It seemed as if the touch I felt was caused by the paintbrush touching the rubber hand
	3. I felt as if the rubber hand was my hand
Disembodiment Questionnaire	**1.** It seemed like I was unable to move my hand
	2. It seemed like I couldn't really tell where my hand was
	3. It seemed like my hand had disappeared

Tactile Detection task

The Tactile Detection task (TD) consisted of 40 randomized tactile stimuli delivered by the experimenter who manually activated the stimulator with a jittering inter-trial-interval (ITI) of 13-15 seconds. We chose such a long ITI to match the timing of the tactile detection task performed before the RHI (TD Pre) with that of the tactile detection task performed in conjunction with the RHI (TD Post), wherein a long ITI (greater than 12 seconds) was required in order for the RHI stroking performed before each stimulus delivery to be effective in inducing the illusion (della Gatta et al., 2016). Hence, stimuli were delivered within a 13-15 second time-window with a jittering onset and without any starting cue signalling stimulus-delivery, to avoid expectancy effects.

During the tactile detection task, participants laid their arms on a desk, with their right hand into the right compartment of the black wooden box and were asked to gaze at the fake hand (see Fig. 17). Moreover, they were made to listen to a white noise track through headphones, whose intensity was adjusted (in a range between 60 and 80 decibels) in order to prevent them from hearing the "click" noise produced by the stimulator; otherwise, this noise could have anticipated to the participants the occurrence of a stimulation. Importantly, the sound intensity was set at the beginning of the experimental session, during threshold estimation (see details in *Electrical stimulation* below), and it was kept constant throughout the session, to avoid possible related confounds. Electrical stimuli were delivered over the hand dorsum and participants were asked to verbally report any tactile sensation and to indicate its location (i.e., "Right hand", "Left hand", "Both hands"). Indeed, 20 stimuli were administered simultaneously to both hands (i.e., bilateral), 10 were administered to the right hand (i.e., unilateral right) and 10 were administered to the left hand (i.e., unilateral left). Note that, since the tactile detection task (as well as the visual detection task, see *Visual detection task*) was specifically designed to test the effect of the experimental manipulation on detection accuracy as in previous studies (Ronga et al., 2018; Swinkels et al., 2020) we added only 5 catch trials in which no stimulation was delivered, to ensure that participants did not respond automatically. During catch trials, the error rate was very low [i.e., in the entire sample (18 participants), only 7 false alarms (4 in the TD Pre and 3 in the TD Post) occurred, leading to 173 correct rejections out of 180 catch trials; moreover, false alarms were present only in 3 participants].

The tactile detection task was performed before the RHI procedure (i.e., TD Pre) to acquire a baseline measure. Then, the RHI procedure started and, after the 2 minutes stimulation (synchronous or asynchronous), the tactile detection task was combined with an RHI stimulation block (13-15 s of synchronous or asynchronous stimulation), so that after each RHI stimulation block one tactile detection trial was performed (i.e., TD Post), for a total of 40 trials (plus 5 catch trials).

Electrical stimulation

Transcutaneous electrical stimulation consisted of constant current square-wave pulses (DS7A, Digitimer) delivered to the hand dorsum, using a pair of surface bipolar electrodes attached to a Velcro strap, as in previous studies (Fossataro et al., 2020). The stimulus duration was 200 µs. Since, during the tactile detection task, we delivered stimuli to the right, to the left or to both hands, we chose to measure the bilateral threshold to set the stimulation intensity so that stimuli would be perceived by both hands. Moreover, we enhanced this intensity by 7% in order to prevent habituation effects, which are normally observed after repetitive stimulation at sensory threshold (Thompson & Spencer, 1966).

To identify participants' bilateral tactile threshold, we employed the method of limits (Gescheider, 1997). Starting from very low magnitude stimulations (1.5-2 mA), the experimenter gradually increased intensity by steps of 0.02 mA until the subject reported a bilateral tactile stimulation. Then, the experimenter lowered the intensity by 0.2 mA until the participant did not report the bilateral stimulation. Hence, the experimenter enhanced the current intensity again, and so on until the electric stimulation intensity which caused participants to report exactly 5 stimuli out of 10 on both hands was determined. The number of trials needed to estimate the threshold varied depending on the subject. During the threshold estimation, as during the tactile detection task, participants wore headphones delivering a white noise as in the TD tasks. The average stimulus intensity of the bilateral threshold in Experiment 1 was (mean ± SD): 3.887 ± 0.972 mA, range 2.41-5.65 mA in the Synchronous condition; 4.092 ± 0.98 mA, range 2.66-5.98 mA in the Asynchronous condition. Importantly, the intensity was not different between conditions (t_{17}=1.641; p=.119).

Experiment 2

Experimental procedure and timeline

Experiment 2 was identical to Experiment 1 except that we investigated the modulations of the visual detection following the RHI. To render the results comparable, the two experiments were designed as closely as possible. However, for the detection tasks, we chose to employ different procedures (e.g., different apparatus, target numbers, target positions) that had been previously devised in our lab for the two modalities (Fossataro et al., *in preparation*; Ronga et al., 2018).

Participants were seated at a desk facing a 21-inches horizontally oriented CRT monitor levelled with the desk plane, at a distance of 50 cm, with each hand resting on the desk, respectively on the left and right sides of the monitor. First, they put their right hand into the covered compartment of the RHI box, and a black tissue covered their shoulders and the proximal parts of their arms (see *Rubber Hand Illusion*). Second, participants' luminance detection threshold was estimated and a visual detection task (VD Pre) was performed. Afterwards, the proprioceptive judgments were collected (Proprioceptive Judgement Pre) and then the 2 minutes RHI (synchronous or asynchronous according to the session) was delivered. Immediately after, the procedure combining the detection task (VD Post) with the 13-15 seconds of RHI stroking was performed (see *Visual Detection Task)*. During the detection tasks and the RHI procedures, participants were asked to look at a central fixation cross on the monitor, below which the rubber hand was placed. Finally, the proprioceptive judgements (Proprioceptive Judgment Post) and the Embodiment and Disembodiment questionnaires were administered, in order to measure whether the procedure was effective in inducing the RHI (see Fig. 17).

Rubber Hand Illusion

The RHI procedure was the same as in Experiment 1, except that participants sat with their arms laying on either side of the horizontally oriented monitor on which the visual stimuli were displayed during the visual detection tasks. The room was scarcely lit so that the same lighting could be used for the visual detection task (see *Visual Detection task*). A different kind of RHI box was designed ad hoc for this experiment. The right hand was covered from view by a dark box (34 cm × 20 cm × 25 cm) while a black piece of tissue concealed the subjects' shoulders and the proximal end of their hands and of the rubber hand. As in Experiment 1, the participants' left hand was aligned with the left shoulder and the fake hand was aligned with the right shoulder, whereas the participant's right hand was externally positioned, 20 cm to the right of the dummy. The fake hand was placed on the monitor so that its index finger laid right below the middle of the screen, where the fixation cross was displayed during the visual detection tasks.

Firstly, an additional box (75 cm × 20 cm × 25 cm) was placed over the previous box and five proprioceptive judgements (Proprioceptive Judgements Pre) were collected. Then, the 2 minutes (synchronous or asynchronous) RHI procedure was performed as in Experiment 1. Immediately after the 2 minutes RHI, the visual detection task (VD Post, see *Visual Detection task*) was carried out, wherein each visual stimulus was preceded by 13-15 seconds of RHI visuo-tactile stimulation. At the end of the VD Post, five proprioceptive judgments (Proprioceptive Judgment Post) and the Embodiment and Disembodiment Questionnaires (for details, see *Rubber Hand Illusion*) were collected to measure the effectiveness of such combined procedure in inducing the RHI.

Visual Detection Task

The Visual Detection task (VD) consisted of 86 randomized trials administered via E-Prime 2.0 software (Psychology Software Tools Inc., Pittsburgh, PA) with a jittering ITI of 13-15 seconds, as in Experiment 1. Subjects were asked to gaze at a white fixation cross displayed in the centre of the screen during the whole task. Visual stimuli (see *Visual Stimuli*) could appear either on the left, on the right or on both sides of the fixation cross, which remained right above the fake hand for the whole task. Before the detection tasks, the fixation cross and the stimuli were displayed on the monitor and we asked participants if they could be detected on screen. Participants were instructed to report the perceived stimuli and to indicate their location on the screen ("Right side", "Left side", "Both sides"). The task consisted of two blocks, which comprised 27 right, 27 left and 27 bilateral trials. Furthermore, we added 5 catch trials, wherein a red fixation cross appeared on screen, and we asked participants to report them by saying "Red". These stimuli were added in order to control that participants gazed at the fixation cross throughout the task. While performing the task, participants listened to a white noise track whose intensity was adjusted (in a range between 60 and 80 decibels), as in Experiment 1.

The detection task was performed before the RHI procedure (VD Pre) to collect a baseline measure of the participants' performance. Afterwards, the RHI procedure began with 2 minutes of RHI visuo-tactile stimulation to induce the illusion. Immediately after, the visual detection task (VD Post) was performed in conjunction with 13-15 seconds of RHI stimulation, so that each trial of the detection task was preceded by 13-15 seconds of RHI stimulation.

Visual stimuli

Visual stimuli consisted of grey rectangles (1 cm × 0.5 cm) appearing on the horizontally oriented 21-inches Sony CRT monitor which was embedded in the desk where participants' hands rested throughout Experiment 2. Stimuli were displayed for 50 milliseconds in 9 different positions: 3 on the left, 3 on the right or bilaterally with respect to a white fixation cross centred on the screen lying right above the fake hand for the entire duration of the experiment. Importantly, in order for the RHI to emerge, the participants' gaze must be directed towards the rubber hand. Hence, in Experiment 2, stimuli were not lateralized with respect to the participants' hands (as in Experiment 1), but, instead, they appeared near the fake hand. We set the luminance intensity slightly above the bilateral threshold level, as in Experiment 1. In order to identify the bilateral luminance threshold, participants performed a visual detection task adapted from Ronga et al. (2018), which comprised 220 visual stimuli divided into 10 successive blocks [for a similar paradigm see also (Sarasso et al., 2018)]. Each block consisted of 18 bilateral and 4 unilateral (randomly left or right) stimuli. The level of luminance across blocks was progressively decreasing (from 2.32% in the first to 1.6% of 226 lux in the last block in steps of 0.08%), so that the difficulty of the task was progressively increasing. Participants were asked to respond by pressing a pedal with their right foot only to bilateral stimuli, ignoring unilateral ones which served as catch trials. Differently from Experiment 1, wherein the experimenter could calibrate the intensity manually, in Experiment 2 the luminance increased in fixed steps across different levels of the threshold visual task. Hence, we decided to define the visual bilateral threshold as the luminance level at which participants reported 60% of bilateral stimuli, to avoid habituation effects. If detection accuracy was higher than 60% in all levels, we adjusted the monitor contrast and brightness and repeated the task to estimate the luminance threshold.

Data Analysis

Experiment 1

Rubber Hand Illusion

To assess whether the RHI procedures successfully modulated the sense of body ownership, we calculated the subjective rating average at the Embodiment and Disembodiment Questionnaire items in both conditions (i.e., Synchronous and Asynchronous). Mean ratings were separately compared between the two conditions as in previous studies [e.g., (della Gatta et al., 2016)], by means of Wilcoxon matched pairs tests.

Furthermore, we calculated the Proprioceptive drift, namely the shift of the felt position of the participant's right hand towards the fake hand (Tsakiris & Haggard, 2005), an additional measure of the RHI that has been demonstrated to be dissociable from the illusory feeling measured by questionnaires (Holmes et al., 2006; Rohde et al., 2011; Tamè et al., 2018). To do so, we averaged the five proprioceptive judgements for each time-point (Proprioceptive Judgment Pre, Proprioceptive Judgment Post) in both conditions (i.e., Synchronous and Asynchronous), and we subtracted the mean of the Proprioceptive Judgments-Post to the mean of the Proprioceptive Judgments-Pre, obtaining a measure of the proprioceptive drift in the Synchronous and in the Asynchronous conditions. Higher values of proprioceptive drift indicated a greater shift towards the fake hand (i.e., a stronger RHI effect). We compared proprioceptive drift values between Synchronous and Asynchronous conditions with a matched pairs t-test. Statistical threshold level was set at α=.05. The RHI analyses, as well as all the following statistical analyses, were performed using Statistica Software (StatSoft, release 8). Note that, following a reviewer's suggestion, for both Experiment 1 and 2, we ran non-parametric tests for discrete measures (i.e., questionnaires) and parametric ones for continuous measures (i.e., proprioceptive drift, detection accuracy – see below).

Tactile Detection task

Detection accuracy analysis. Statistical analyses were performed on the percentage of correct responses (i.e., detection accuracy).

In our *main analysis* we investigated the presence of a RHI-dependent effect on tactile accuracy and whether such a modulation was circumscribed to the hand subjected to the illusion, including both unilateral and bilateral trials in a single analysis, by categorizing the data as follows. When participants responded “left hand” to a left-hand unilateral stimulation, we considered that as a correct response for left-hand trials. When participants responded “right hand” to a right-hand unilateral stimulation, we considered that as a correct response for right-hand trials. When participants responded “left hand” to a bilateral stimulation, we considered that as a correct response for left-hand trials and as an incorrect response for right-hand trials. When participants responded “right hand” to a bilateral stimulation, we considered that as a correct response for right-hand trials and as an incorrect response for left-hand trials. When participants did not respond to a unilateral (left- or right-hand) stimulation, we considered that as an incorrect response for the corresponding trial. When participants did not respond to a bilateral stimulation, we considered that as an incorrect response for both right-hand and left-hand trials. Hence, we entered tactile detection accuracy in a 2 × 2 × 2 repeated-measures ANOVA with Condition (Synchronous, Asynchronous), Time (TD Pre, TD Post) and Side (Left-hand, Right-hand) as within subject factors. Post hoc comparisons were carried out by means of Newman-Keuls’ test. Statistical threshold level was set at α=.05.

Furthermore, we run *additional analyses*, performed separately on unilateral and bilateral tactile detection accuracy, with the aim of investigating whether the modulatory effects were present both in unilateral and bilateral trials. Specifically, we performed two 2 × 2 × 2 repeated-measures ANOVA with Condition (Synchronous, Asynchronous), Time (TD Pre, TD Post) and Side (Left-hand, Right-hand) as within subject factors on each dataset. Post hoc comparisons were carried out by means of Newman-Keuls’ test. Since the data were split in two separate analyses, statistical threshold level was set at α=.025.

Note that our main analyses were performed following a Reviewer suggestion, whereas the additional analyses were planned a priori.

Correlational analysis. We ran Spearman correlations between RHI measures (Embodiment and Disembodiment questionnaires' mean ratings, proprioceptive drift values) and a modulation index, calculated as the % of tactile detection accuracy in the TD Post – % TD Pre on the Right-hand trials of the Synchronous and Asynchronous conditions.

Experiment 2

Rubber Hand Illusion

To compare the RHI measures (mean of subjective ratings to the Embodiment and Disembodiment questionnaires, proprioceptive drift) between synchronous and asynchronous conditions, we employed the very same analyses of Experiment 1 (see *Rubber Hand Illusion*). Statistical threshold level was set at α=.05.

Visual detection task

Detection accuracy analysis. To investigate the RHI effect on visual stimuli detection we calculated the percentage of correct responses (i.e., visual detection accuracy) for each condition in the VD Pre and in the VD Post task. We then entered these values in a repeated-measures 2×2 ANOVA with Condition (Synchronous, Asynchronous) and Time (VD Pre, VD Post) as within-subject factors. Post hoc comparisons were carried out by means of Newman-Keuls' test. Statistical threshold level was set at α=.05.

Correlational analysis. We ran Spearman correlations between RHI measures (Embodiment and Disembodiment questionnaires' mean ratings, proprioceptive drift values) and a modulation index, calculated as the % of visual detection accuracy in the VD Post – % VD Pre of the Synchronous and Asynchronous conditions.

Results

Experiment 1

Rubber Hand Illusion

The Wilcoxon tests comparing Synchronous vs Asynchronous conditions revealed a significant difference both for the Embodiment (T=0; p=.0003; effect size r=.604; Fig. 18 panel A) and the Disembodiment questionnaire (T=18; p=.017; r=.384; Fig. 18 panel B), showing, as expected, greater values in the Synchronous as compared to the Asynchronous condition. Note that, although participants showed a general tendency to give lower ratings to the items of the Disembodiment than to those of the Embodiment questionnaire, overall they attributed higher scores in the synchronous as compared to the asynchronous condition in both cases. Furthermore, the t-test between Synchronous and Asynchronous conditions on the proprioceptive drift measures revealed a significant difference between conditions (t=2.198; p=.042; dz=0.516; Fig. 18 panel C). Indeed, as expected, the Synchronous condition's shifts were greater than the Asynchronous' ones.

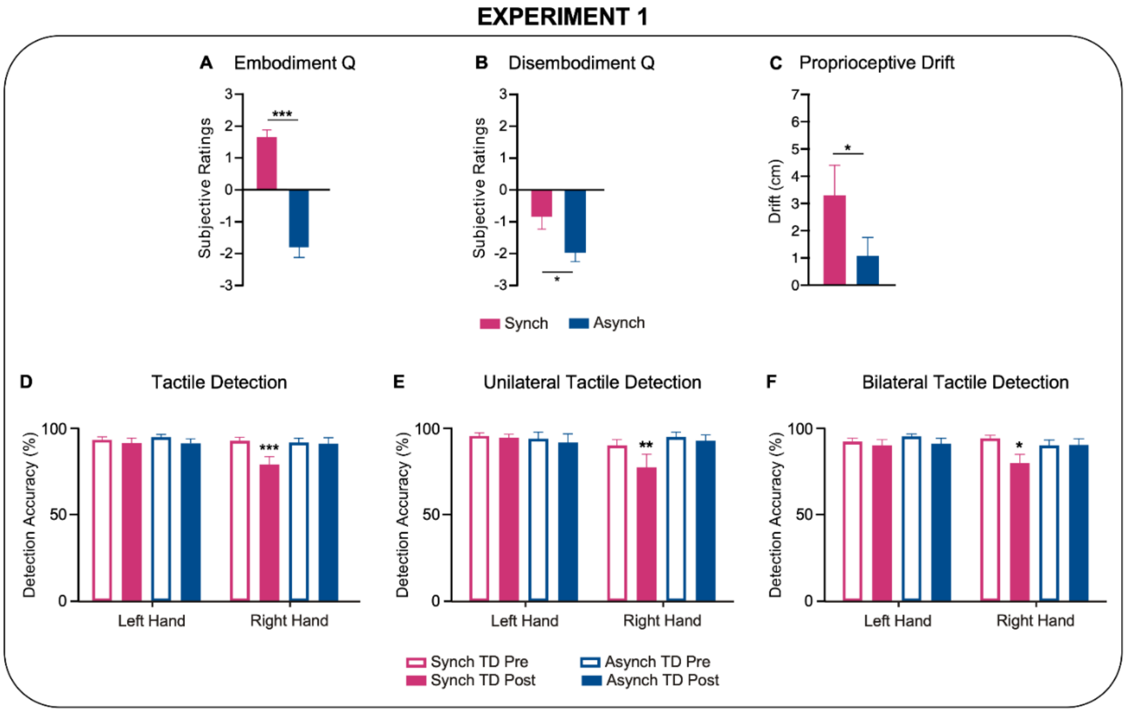

Fig. 18 Results of Experiment 1 (A) Embodiment Questionnaire results: mean embodiment ratings (Likert Scale -3/+3). **(B)** Disembodiment Questionnaire results: mean disembodiment ratings (Likert Scale -3/+3). **(C)** Proprioceptive Drift results: mean drift (cm) towards the fake hand. Note that in (A) and (B) higher values indicate a greater agreement with the questionnaire items and in (C) higher values indicate greater

shifts towards the fake hand. In (A), (B) and (C) a significant difference is present between Synchronous and Asynchronous conditions, with greater values in the former than in the latter. **(D)**, **(E)** and **(F)** respectively show tactile detection accuracy (%) calculated merging unilateral and bilateral data **(D)**, unilateral tactile detection accuracy (%) **(E)**, and bilateral tactile detection accuracy (%) **(F)** in the Synchronous (pink) and Asynchronous (blue) conditions, in the TD Pre (empty plot) and in the TD Post (solid plot) for the right- and left-hand stimulations. In (D), (E) and (F), detection accuracy of right-hand's stimuli is significantly lower, after the Synchronous RHI. Note that, when correction for multiple comparison was applied, the results of the analysis performed on unilateral data (E) did not reach statistical significance (Condition × Time × Side interaction: $p=.049$; $\alpha=.025$). * =$p<.05$; ** =$p<.005$ *** =$p<.0005$ (uncorrected). Bars indicate standard errors of the mean (SEM).

Tactile Detection task

Detection accuracy analyses. The *main analysis* showed a significant main effect of Time ($F_{1,17}=14.633$; $p=.001$; $\eta^2_p=.463$) and a significant Condition × Time interaction ($F_{1,17}=17.808$; $p=.001$; $\eta^2_p=.512$). Crucially, we also found a significant Condition × Time × Side interaction ($F_{1,17}=11.175$; $p=.004$; $\eta^2_p=.397$). In particular, the Synchronous TD Post Right-hand condition showed a significantly lower tactile detection accuracy relative to the Synchronous TD Pre Right-hand ($p=.0003$; $dz=1.063$) and all the other conditions (p always$<.0005$; see 17 panel D). Conversely, no significant differences resulted between Asynchronous conditions, nor between Synchronous Pre and Asynchronous Pre or Post conditions (p always $>.514$).

When separate analyses were run on unilateral and bilateral trials (*additional analyses*), similar results were found. Specifically, results of unilateral data highlighted not only a significant main effect of Time ($F_{1,17}=9.142$; $p=.008$; $\eta^2_p=.350$), but also a Condition × Time × Side interaction ($F_{1,17}=4.503$; $p=.049$; $\eta^2_p=.209$), with the Synchronous TD Post Right-hand condition showing significantly lower tactile detection accuracy relative to the Synchronous TD Pre Right-hand ($p=.0004$; $dz=0.650$) and all the other conditions (p always$<.001$; see 17 panel E). Conversely, no differences were highlighted between Asynchronous conditions, nor between Synchronous Pre and Asynchronous Pre or Post conditions (p always $>.480$). Furthermore, results of bilateral data highlighted not only a significant main effect of Time ($F_{1,17}$=7.630; p=.013; η^2_p=.310) and a significant a Condition × Time interaction ($F_{1,17}$=14.647; p=.001; η^2_p=.463), but, crucially, also a significant Condition × Time × Side interaction ($F_{1,17}$=7.692; p=.013; η^2_p=.312). Post hoc tests revealed that the Synchronous TD Post Right-hand condition showed significantly lower tactile detection accuracy relative to the Synchronous TD Pre Right-hand (p=.003; dz=0.860) and all the other conditions (p always<.01; see 17 panel F). Conversely, no differences were found between Asynchronous conditions, nor between Synchronous Pre and Asynchronous Pre or Post conditions (p always >.480).

However, while the results of bilateral data highlighted significant results, the Condition × Time × Side interaction found in the unilateral data analysis did not reach statistical significance when the correction for multiple comparison was applied (α=.025). We reasoned that this result could be due to the lower number of unilateral trials (20 total: 10 right-hand, 10 left-hand) and thus recommend a minimum of 40 trials (40 total: 20 right-hand, 20 left-hand) for future studies that will capitalize on detection paradigms like the one employed here.

Correlational analysis. No significant correlation was found between RHI measures and the modulation index (p always >.05), highlighting that the relationship between changes in ownership and tactile downregulation was not linear.

Experiment 2

Rubber Hand Illusion

The Wilcoxon tests comparing the Embodiment and Disembodiment questionnaire's mean ratings between conditions showed a significant difference (Embodiment: T=1; p=.0002; r=.613; Disembodiment: T=20.5; p=.014; r=.409; Fig. 19 panel A&B) with higher values in the Synchronous than in the Asynchronous condition. Coherently, the t-test which compared PD measures in the Synchronous and Asynchronous conditions revealed a significant difference between conditions (t=3.164; p=.140; dz=0.746; Fig. 19 panel C), with the former showing greater values than the latter.

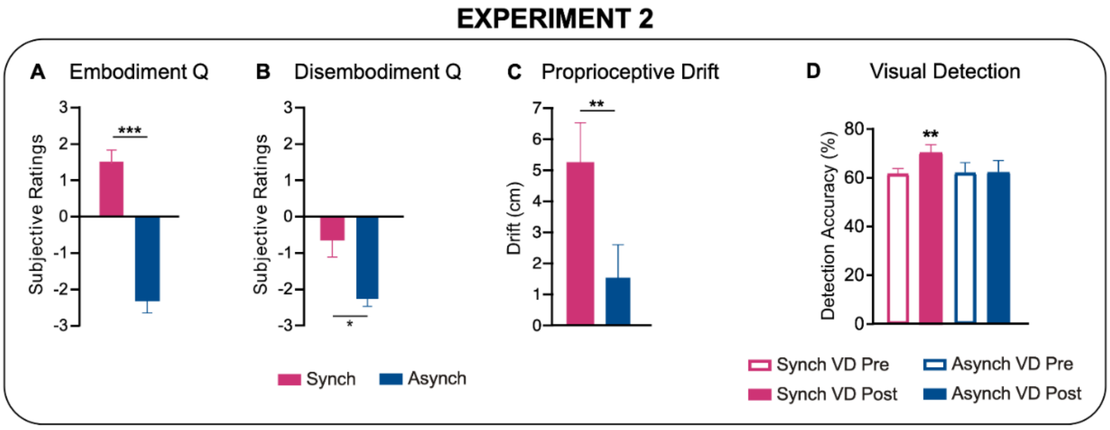

Fig. 19 Results of Experiment 2 (A) Embodiment Questionnaire results: mean embodiment ratings (Likert Scale -3/+3). **(B)** Disembodiment Questionnaire results: mean disembodiment ratings (Likert Scale -3/+3). **(C)** Proprioceptive Drift results: mean drift (cm) towards the rubber hand. In (A), (B) and (C) a significant difference is present between Synchronous and Asynchronous conditions, with greater values in the former than in the latter. **(D)** shows the visual detection accuracy (%) in the Synchronous (in pink) and Asynchronous (in blue) conditions, in the VD Pre (empty plot) and in the VD Post (solid plot). Detection accuracy is significantly higher after the Synchronous RHI. * =p <.05; ** =p<.01; *** =p<.0005. Bars indicate standard errors of the mean (SEM).

Visual Detection task

The repeated-measures ANOVA showed a significant main effect of Time ($F_{1,17}$=4.527; p=.048; η^2_p=.210), with higher accuracy in VD Post than in VD Pre. Crucially, we also found a significant Condition × Time interaction ($F_{1,17}$=9.078; p=.008; η^2_p=.348). In particular, the Synchronous VD Post condition showed a significantly higher visual detection accuracy relative to the Synchronous VD Pre condition (p=.002, dz=0.756) and all the other conditions (p always<.003; see Fig. 19 panel D). Conversely, the Asynchronous VD Post condition did not differ from the Asynchronous VD Pre condition (p=.916; dz=0.023).

Correlational analysis. No significant correlation was found between RHI measures and the modulation index (p always >.05), pinpointing that the relationship between dis(embodiment) and visual upregulation was not linear.

Discussion

In this study, we investigated whether, after the RHI, a modulation of tactile and visual processing occurs using a perceptual threshold stimulation paradigm, to better understand the mechanisms underpinning the updating of the SBO. To manipulate the sense of body ownership in healthy participants, we employed the RHI paradigm (Matthew Botvinick & Cohen, 1998a). In two separate experiments, to investigate the body ownership-dependent modulation of tactile (Experiment 1) and visual (Experiment 2) processing, we employed two detection tasks performed before and after the RHI, wherein we administered stimuli slightly above the participants' perceptual threshold level.

The results of both Experiment 1 and 2 demonstrate that the RHI modulated the sense of body ownership. Indeed, we found significantly higher scores in the Synchronous than in the Asynchronous condition of the classical RHI measures (i.e., Embodiment and Disembodiment Questionnaires, proprioceptive drift). Although dummy items that control for general suggestibility were not included in the questionnaires, we show converging evidence using different RHI measures, highlighting that the (dis)embodiment effect was present only in the synchronous condition. Interestingly, proprioceptive drift resulted almost double in Experiment 2, as compared to Experiment 1. This may be explained by individual differences between the two samples. However an alternative interpretation could be that in Experiment 1, after each trial of the detection task, proprioception may be recalibrated onto the real hand position due to the tactile stimulation. Conversely, in Experiment 2, visual stimuli delivery should not result in proprioceptive recalibration. Crucially, the results show that, after the RHI, a diametrical effect on tactile and visual accuracy is observed, with a decreased detection of tactile stimuli delivered on the real hand and an increased detection of visual stimuli delivered around the fake hand.

In the tactile domain, a detection decrease following the RHI has already been demonstrated with unilateral threshold stimuli (Zopf et al., 2011) or employing unilateral above-threshold stimuli (Folegatti et al., 2009), but neither of these studies directly verified whether this effect was circumscribed to the hand subjected to the illusion. In Experiment 1, the results of the main analysis reveal that, only when body ownership is modulated (i.e., in the Synchronous condition), tactile detection accuracy is diminished. Interestingly, we found a differential effect between the stimulation of the right and the left hand, revealing that the decrease of somatosensory detection is circumscribed to the hand exposed to the illusion (i.e., the right hand). Importantly, we were able to rule out that this difference was due to the fact that participants could see the left but not the right ("illuded") hand throughout the task (Tipper et al., 1998, 2001), because no difference between right- and left-hand stimuli detection was found in the baseline task (i.e., TD Pre), in which the RHI stimulation was not applied. Furthermore, our results on bilateral detection are original, since no previous study investigated the effect of the RHI on bilateral stimulations. Crucially, we show that in bilateral trials participants tend to selectively omit the stimulation directed to the hand subjected to the illusion after the induction of the RHI. A similar omissive behaviour has been extensively described in brain-damaged patients with tactile extinction [TE; e.g. see (Chechlacz et al., 2013; Chechlacz et al., 2013; Eimer et al., 2002; Fossataro et al., 2020; Neppi-Modona, 1999; Vallar et al., 1994)], namely a neuropsychological deficit that consists in a failure in detecting contralesional tactile stimuli when simultaneously delivered with competing ipsilesional ones. Since these patients show normal detection of unilateral ipsilesional and contralesional stimuli, revealing spared somatosensory processing in the affected limb, TE has been interpreted as an ipsilesional bias in the orientation of spatial attention (Bisiach & Vallar, 2000; Driver & Vuilleumier, 2001; Heilman et al., 2000; Jacobs et al., 2011). Several works have addressed extinction-like behaviour in healthy participants, either inducing "virtual lesions" employing non-invasive brain stimulation [for a review see (Oliveri & Caltagirone, 2006)], or employing cross-modal (Colavita, 1974; Filbrich et al., 2019; Jacobs et al., 2011; Ronga et al., 2012; Spence, Parise, & Chen, 2011) or unimodal (Farnè et al., 2007) detection paradigms. During these experimental manipulations, despite normal detection in unilateral trials, an impaired tactile detection emerged during bilateral stimulations. By contrast, in our study we observe a decrease of tactile detection also in right-hand unilateral trials, suggesting that, here, pseudo-extinction likely occurs as a side effect of the modulation of the right-hand unilateral threshold.

Despite the converging evidence on the effects of the RHI on the somatosensory system, the modulations induced in the visual system seem to be less investigated in literature, and previous findings are controversial. A behavioural study by Longo and colleagues showed that the RHI enhances the perceived physical similarity between the real and the fake hand (Longo et al., 2009), demonstrating a detriment of visual processing after the RHI. On the other hand, Van Der Hoort and colleagues (Van Der Hoort, Reingardt, & Ehrsson, 2017) indicate that the saliency of the visual input is somehow enhanced by the embodiment of a virtual hand. They addressed whether the embodiment of a virtual hand affects visual awareness in a binocular rivalry paradigm. The authors manipulated the sense of body ownership by applying visuo-tactile stimulation onto the participants' real hand while observing two rival images: a hand and a mask image that randomly alternated at 10 Hz. The authors found that the amount of time wherein participants were able to see the hand image despite the presence of the mask increased only when the participants' body ownership was manipulated. According to this latter study, the Experiment 2 results show that participants' performance in a visual detection task is significantly improved after the modulation of body ownership (i.e., VD Post of the Synchronous condition). To our knowledge, our study is the first to test the visual system modulation during the RHI, measuring the perceptual threshold as a behavioural correlate of visual processing. This novel finding indicates that the embodiment of a dummy hand influences the perceptual processes in the tactile and visual domains in diametrical directions.

It has been proposed that the neural mechanism through which the brain settles the multisensory conflict generated during the synchronous RHI relies on the contribution of 1) a downregulation of the weight attributed to somatosensory information, reflected here by the reduction of tactile detection 2) an upregulation of the weight attributed to visual information, reflected here by the reduction of visual detection (Limanowski & Blankenburg, 2016; Zeller et al., 2016). Why should our brain rely more on visual rather than somatosensory inputs when they are incongruent? According to the predictive coding account, from time to time, the central nervous system (CNS) explains away conflicting proprioceptive and visual information by estimating the precision of each modality and thus adjusting the weight attributed to each sensory input to minimize estimation errors (Ronga et al., 2017; van Beers, Sittig, & Gon, 1999; van Beers, Wolpert, & Haggard, 2002). In other words, the CNS determines the signal-to-noise ratio of each input, according to current experience (e.g., evaluating the congruency between different sources of information) and to acquired knowledge (e.g., some aprioristic factors, such as the generally higher amount of noise present in proprioceptive as compared to visual information). As an example, it has been demonstrated that, when there is a small visuo-proprioceptive disparity (e.g., ≤10°), the CNS tends to rely on visual input, which is considered less noisy and therefore more precise in the exact determination of locations in space (Ernst & Banks, 2002). Whereas, under a condition of large disparity (e.g., >20°), namely when the incongruency cannot be attributed to the lower signal-to-noise ratio of proprioceptive information, proprioception overcomes the visual input (Fang et al., 2019; Fossataro, et al., 2020). In line with these results, it is well-known that in the classical RHI setting, when the fake hand is in an anatomically plausible position (i.e., a small disparity is present), vision of the fake hand largely dominates over proprioception so that the tactile sensation is remapped onto the fake hand and the illusion arises. Conversely, when the fake hand is in an anatomically implausible position relative to the participants' posture (i.e., a large disparity is present), proprioception can overcome vision preventing subjects to experience the illusion [e.g., see (Fang et al., 2019; Ide, 2013; Kalckert et al., 2019; Kalckert & Ehrsson, 2014)]. Therefore, provided the discrepancy is within reasonable limits, during the RHI visual inputs seem to overcome somatosensory inputs, because the visual system can compute a less noisy (i.e., more reliable) estimation of one's own hand. As a supporting evidence, Ronga et al. (Ronga et al., 2017) showed that, when the brain judges visual input as more noisy than proprioception (as it happens for a special kind of prismatic adaptation performed through eye-movements, precluding the view of the own body), a proprioception capture of vision is observed (i.e., the conflict between vision and proprioception is resolved in favour of proprioception). If visual dominance occurs in the context of the RHI because the variance associated with visual estimation is lower than that associated with proprioceptive estimation (Ernst & Banks, 2002), one should observe that, when visual input is rendered noisier, somatosensory inputs overcome visual inputs. Future studies could test this interpretation by experimentally making visual input noisier, hence overturning the balance between visual and proprioceptive input's noisiness.

One final issue should be discussed, that is the role of attentional processes in the RHI. In both Experiments, the participant's focus of attention was directed towards the target modality, because the task required to detect tactile or visual stimuli. Hence, the effect highlighted here cannot be explained by low-level attentional factors such as the simple presence of a fake hand in the visual scene, otherwise between-condition differences would not be observed. Nevertheless, it is possible that embodiment-dependent modulations (i.e., modulations that are present only after the synchronous RHI) may be mediated by attention. Attentional factors likely play a major role in the modulation of visual and tactile inputs when an incongruency between multiple sensory inputs occurs (Limanowski & Friston, 2019, 2020; Talsma et al., 2010). According to the maximum-likelihood estimation model, somatosensory and visual inputs are integrated by weighting each single modality relative to its estimated precision, in order to obtain the most reliable multisensory prediction (Ernst & Banks, 2002; Ernst & Bülthoff, 2004). Given that attention has been associated with top-down modulation of sensory precision estimate (Limanowski & Friston, 2019, 2020), it is very likely that attentional shifts towards the fake hand contribute to mediate the influence of embodiment on sensory processing. However, further research is needed to isolate the specific contribution of attention in such processes.

Despite the evidence that we provide, some limitations of the study need to be addressed. First, the detection tasks employed for the tactile (Experiment 1) and visual (Experiment 2) modalities show methodological differences, hence no direct comparison could be made between experiments. Second, given the impossibility of applying the Signal Detection Theory (Stanislaw, 1999) to the present data, we cannot dissociate detection changes from other changes, i.e., response bias. Further studies are needed to address this specific issue.

Conclusion

To sum up, the present study describes a body ownership-dependent diametrical modulation of tactile and visual perceptual thresholds following the RHI, with decreased tactile and increased visual detection performances. Under normal circumstances, visual and somatosensory inputs provide congruent information to higher-order integrative cortices that implement them in a unitary and coherent representation of one's own body. Employing experimental procedures, such as the RHI, aimed to generate a multisensory mismatch, can shed light on the neural mechanism through which our brain plastically adapts to uncertainty by attributing differential weights to each source of sensory information, according to its expected and prior reliability values. Here we provide original behavioural evidence that, during the RHI, the alteration of the sense of body ownership relies both on the attenuation of somatosensory inputs coming from one's own hand and on the enhancement of visual perception around the fake hand. The diametrical pattern of our results strongly supports the view that, during the RHI, the weight attributed to somatosensory information is decreased while that of visual information is increased, in line with previous findings discussed above. Taken together, the two experiments described here confirm and expand on previous knowledge about the RHI effect in the somatosensory system and provide the very first behavioural evidence of a modulation of the visual system as a consequence of the alteration of the sense of body ownership, in line with the predictive coding framework.

Study 2.2: Balancing somatosensory and visual afferences in face of a multisensory conflict: the case of embodiment

[This research is currently in preparation as Rossi Sebastiano A., Fossataro C., Poles K., Gualtiero S., Ronga I., Garbarini F., Balancing somatosensory and visual afferences in face of a multisensory conflict: the case of embodiment]

Introduction

As stated at the beginning of this chapter, the multisensory conflict emerging from the synchronous RHI likely generates a prediction error (Friston, 2005), which is resolved by the brain to restore a coherent representation of one's own body (Apps & Tsakiris, 2014; Limanowski & Blankenburg, 2013). Study 2.1 provided compelling evidence that its neural mechanism relies on two processes: on one hand the weight attributed to somatosensory inputs is downregulated, on the other hand the weight attributed to visual inputs is increased. These processes should result from the activity of high-order parieto-premotor multisensory cortices that receive afferent sensory input from primary cortices, detect the mismatch between visual and tactile information and settle the visuo-tactile conflict. Although the contribution of multisensory cortices as the neural signature of the illusory feeling of embodiment has largely been demonstrated (Brozzoli et al., 2012; Casula et al., 2022; Ehrsson et al., 2004, 2005; Gentile et al., 2015; Golaszewski et al., 2021; Limanowski & Blankenburg, 2015; Petkova et al., 2011), the involvement primary sensory areas is still controversial. As concerns somatosensory cortices, behavioural evidence suggests attenuated somatosensory processing, after the illusion induction (Folegatti et al., 2009; Rossi Sebastiano et al., 2021; Zopf, Harris, et al., 2011). Coherently, recent electrophysiological studies, based on the analysis of touch-evoked potentials during the RHI, suggest that the somatosensory cortex activity may be down-regulated (Sakamoto & Ifuku, 2021; Zeller et al., 2015).

Conversely, the evidence concerning the visual cortices modulation during the RHI is sparse. In Study 2.1, we previously demonstrated a diametrical modulation of tactile and visual detection thresholds, with the former being attenuated and the latter enhanced following the illusion induction (Rossi Sebastiano et al., 2021). Here, we sought to shed light on how the brain balances the processing of somatosensory and visual afferences, providing evidence of the neural mechanism that enables embodiment and disembodiment. To this aim, the amplitude of somatosensory (SEPs; Experiment 1) and visual (VEPs; Experiment 2) evoked potentials was measured following either synchronous or asynchronous (control) RHI, with reference to a baseline condition.

Methods

Participants

Since we planned to perform a two-tailed t-test between synchronous and asynchronous conditions as main analysis, we computed the required sample size based on the contrast between post-RHI detection in the synchronous and asynchronous condition of our previous behavioural data [see Experiment 1 in (Rossi Sebastiano et al., 2021)], by employing G*Power software. A sample of 18 participants was estimated [$\alpha=0.05$; power $(1-\beta)=0.92$; $dz=0.87$], coherently with previous electrophysiological studies on RHI-related effects on the somatosensory system that employed samples between 14 and 18 subjects (Rao & Kayser, 2017; Sakamoto & Ifuku, 2021; D. Zeller et al., 2015). Hence, two different samples of 18 participants were recruited [Experiment 1: 10 women, age (mean±sd) = 25±3.65, education level = 15.83±2.64; Experiment 2: 9 women, age = 26.79±3.05, education level = 17.79±0.42]. Note that, in Experiment 1, 3 participants dropped out before the baseline session, and in Experiment 2, 1 participant missed the synchronous session. All participants were right-handed according to the Edinburgh Handedness Inventory (R. C. Oldfield, 1971), had normal tactile sensitivity and normal (or corrected-to-normal) visual acuity. They all gave informed consent to participate in the study, which was approved by the Ethical Committee of the University of Turin (prot. n°122571).

Experimental procedures

In the present study we employed electroencephalography to collect event-related potentials to somatosensory (Experiment 1) and visual (Experiment 2) stimuli, following the RHI. The experimental procedure was identical for the two experiments, except for the sensory modality being tested (see Fig. 20). Participants underwent three experimental sessions, wherein they performed either the synchronous, the asynchronous or the baseline condition. The sessions' order was randomized among subjects. Each session comprised two identical blocks, in which 50 trials were administered (total: 100 trials). In between blocks participants made a 5-minute break to rest. Each trial consisted of a combined procedure comprising 12 s of synchronous, asynchronous RHI or no stimulation (baseline), immediately followed by the delivery of 10 subsequent somatosensory (Experiment 1) or visual (Experiment 2) stimuli at a frequency of 1.5 Hz (total: 1000 stimuli per condition). Hence, while in the RHI conditions stimuli delivery was alternated with 12 s of either synchronous or asynchronous RHI and participants always gazed at a fixation cross immediately in front of the rubber hand (see *Combined RHI and stimulation procedure*), in the baseline stimuli delivery was alternated with a 12 s rest period wherein participants observed the fixation cross located in the empty RHI box. At the end of each RHI block Embodiment and Disembodiment questionnaires were collected (see *Combined RHI and stimulation procedure*).

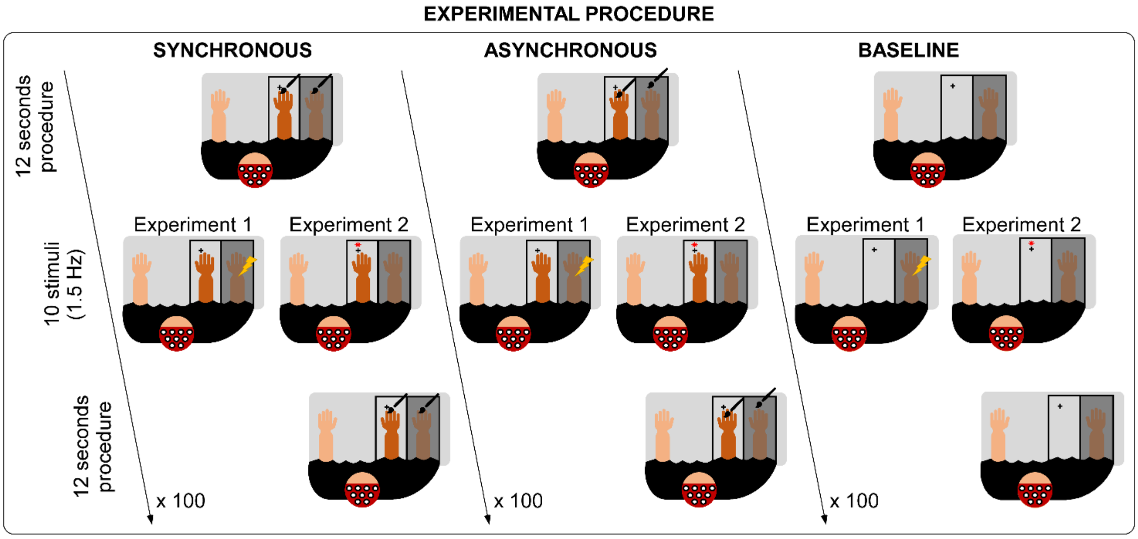

Fig. 20: experimental procedure. The figure depicts the experimental procedures of Experiment 1 and 2. The darker hand represents the rubber hand, whereas lighter hands represent the participant's hands. The

combined RHI and stimulation procedure consisted in alternating 12 s of synchronous, asynchronous RHI or rest (according to the condition) with the delivery of a train of 10 stimuli (stimulus sensory modality: somatosensory in Experiment 1, visual in Experiment 2). Participants underwent 2 blocks of 50 trials (total: 100 trials).

Combined RHI and stimulation procedure

The experimental materials used for the RHI procedure comprised a black wooden box (60 cm × 40 cm × 20 cm), a black piece of tissue and two realistic rubber hands (male and female). The box was divided into two compartments: the right one was covered by a black panel, while the top of the left compartment was open. At the beginning of the session, participants sat comfortably at a desk in a dimly lit room and placed their right hand into the corresponding compartment of the box, so as to hide it from view. In the RHI sessions, the fake hand (male or female, according to the subject's gender) was positioned inside the left open compartment, to make the fake hand visible. The participant's left hand was aligned with the left shoulder and the fake hand was aligned with the right shoulder, whereas the participant's right hand was externally positioned, 20 cm to the right of the fake hand. We took care that the fake hand was placed in an anatomically congruent position from the participant's egocentric perspective and that the black piece of tissue covered the shoulders and the proximal portions of the real and the dummy hand.

In the RHI conditions, 12 s of RHI procedure were performed before each train of 10 stimuli. In the *synchronous* RHI condition, wherein the illusion generally occurs, the experimenter stroked the participant's hand synchronously with the rubber hand. Conversely, in the *asynchronous* condition, wherein the illusion generally does not occur (i.e., control condition), the experimenter stroked the participant's hand in anti-phase with the rubber hand. Participants were asked to gaze at a fixation cross which was placed immediately in front of the index finger of the rubber hand.

Note that, in the baseline condition, the rubber hand was removed from the left compartment of the box and participants did not receive any stroking. Thus, in this condition, participants just observed the fixation cross, which was in the same position as in the RHI conditions.

At the end of each block, participants rated 1) their subjective feeling of ownership over the fake hand by answering to three items of the Embodiment questionnaire (Botvinick & Cohen, 1998; Fossataro et al., 2018, see Table 1) and 2) their subjective feeling of disownership over their real hand by answering to three items of the Disembodiment questionnaire (Longo et al., 2008; Fossataro et al., 2018, see Table 5). They were asked to rate their agreement with these items on a 7 points Likert Scale, ranging from "-3" ("strongly disagree") to "+3" ("strongly agree").

TABLE 5 Embodiment and Disembodiment questionnaires (Fossataro et al., 2018; Longo et al., 2008) Participants were asked to rate their agreement with the following statements by assigning a score to each item, using a 7 points Likert Scale (-3 = "strongly disagree"; +3 = "strongly agree").

Embodiment Questionnaire	**1.** It seemed as if I were sensing the touch in the location where I saw the rubber hand touched
	2. It seemed as if the touch I felt was caused by the paintbrush touching the rubber hand
	3. I felt as if the rubber hand was my hand
Disembodiment Questionnaire	**1.** It seemed like I was unable to move my hand
	2. It seemed like I couldn't really tell where my hand was
	3. It seemed like my hand had disappeared

Experimental stimuli

Somatosensory stimuli (Experiment 1) Somatosensory stimulation consisted in transcutaneous electrical stimuli through constant current square-wave pulses (Digitimer D7AH) delivered over the right median nerve, using a pair of surface bipolar electrodes attached to a Velcro strap. Stimulus duration was 200 μs. Stimulus intensity was set at the 110% of the motor threshold, defined as the minimum stimulation intensity able to elicit a thumb twitch.

Visual stimuli (Experiment 2) Visual stimulation consisted in brief flashes through a red light emitting diode (LED) (Creel, 2019) of 5 mm. Stimulus duration was 5 ms. The LED was mounted immediately in front of the fixation cross, so that participants could see both the rubber hand and the LED during the RHI sessions.

Experimental design and statistical analysis

The present study shows two experiments (one investigating the somatosensory modality – Experiment 1, one investigating the visual modality – Experiment 2) with identical within-subject designs, consisting in three conditions: synchronous RHI, asynchronous RHI, baseline. Please find below the detailed description of the performed statistical analyses.

Behavioural analyses

For both Experiment 1 and 2, mean ratings attributed to the Embodiment and Disembodiment questionnaires were separately compared between synchronous and asynchronous conditions by means of a Wilcoxon matched-pairs t-test (Shapiro Wilk's test on residuals: $p<0.05$).

EEG recording and preprocessing

ERPs were recorded through 32 Ag-AgCl active electrodes (International 10–20 system) referenced to the nose. Electrode impedances were kept below 5 kΩ. To track ocular movements and eye blinks, the electrooculogram was recorded by two surface electrodes, one placed over the right lower eyelid and the other placed lateral to the outer canthus of the right eye. Continuous EEG was recorded using a HandyEEG SystemPLUS Evolution amplifier (Micromed) at a 2048 Hz sampling rate. Off-line EEG preprocessing and analyses were performed with Letswave6 toolbox (Nocions, Louvain, Belgium) for Matlab (Mathworks, Natick, MA). The EEG signal was segmented into epochs lasting from 100 ms before to 500 ms after stimulus delivery (total epoch duration: 600 ms). Epochs were band-pass filtered (1-100 Hz) using a Butterworth filter (order 3), and then baseline corrected using as reference a signal period from 100 to 20 ms prior to the stimulus delivery. Artifacts due to eye blinks and eye movements were subtracted using a validated method based on an Independent Component Analysis [ICA – (Jung et al., 2000)]. Blinks were found to be the most frequent cause of rejection. Finally, epochs belonging to the same experimental condition (1000 trials for each condition) were averaged, thus yielding three average waveforms, one for each condition (synchronous, asynchronous, baseline).

ERP analyses

To analyse the ERP amplitude, we performed point-by-point statistics that allow to highlight significant amplitude differences and possible latency-shifts at the same time, comparing all time points between experimental conditions. Since this whole-brain analysis performs one comparison per time point separately on each electrode, the results must be corrected for multiple comparisons through a cluster-based permutation test (1000 random permutations) (Galigani et al., 2021; Irene Ronga et al., 2021).

In the main analyses, to compare ERPs between the condition wherein embodiment is elicited and the control one, we performed a matched-pairs t-test between synchronous and asynchronous conditions.

Furthermore, we ran additional analyses to verify whether the possibly observed modulations in the RHI conditions were in the direction of a down- or an up-regulation with reference to the baseline response to stimuli. Hence, for each experiment, we ran two matched-pairs t-test, comparing each RHI condition to the baseline.

Correlational analyses

Moreover, we extracted the mean amplitude from central (in Experiment 1, wherein somatosensory activity was investigated) and occipital (in Experiment 2, wherein visual activity was investigated) electrodes in the time-windows wherein a difference between conditions was observed. In Experiment 1, we calculated a *downregulation index*, computed as the mean amplitude in the synchronous minus the mean amplitude in the asynchronous condition. In Experiment 2, we calculated an *upregulation index*, computed as the mean amplitude in the synchronous minus the mean amplitude in the asynchronous condition. Based on the subjective ratings that participants attributed to the items of both the Embodiment and the Disembodiment questionnaires, we calculated 1) an embodiment index, computed as the mean rating in the synchronous minus the mean rating in the asynchronous condition; 2) a disembodiment index, computed as the mean rating in the synchronous minus the mean rating in the asynchronous condition. For each experiment, we ran two Pearson correlations, one between the amplitude index and the embodiment index, one between the amplitude index and the disembodiment index. Since we performed two comparisons for each questionnaire, the Bonferroni-corrected statistical threshold was $\alpha=0.025$. These analysis allowed to establish whether the difference between the ERPs elicited following synchronous and asynchronous RHI correlated with the subjective level of embodiment and disembodiment.

Results

Experiment 1

Behavioural analyses

The Wilcoxon tests revealed a significant difference between condition for both Embodiment ($T_{17}=0$; Z=3.72; p=0.0002) and Disembodiment ($T_{17}=4$; Z=3.31; p=0.001) questionnaires, with higher values in the synchronous as compared to the asynchronous condition. See Fig. 21.

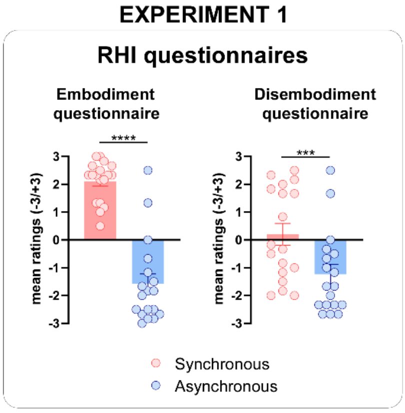

Fig. 21: rubber hand illusion results of Experiment 1. Embodiment Questionnaire results: mean embodiment ratings (Likert Scale − 3/+ 3). Disembodiment Questionnaire results: mean disembodiment ratings (Likert Scale − 3/+ 3). Dots represent each participant's value, bars represent the standard error of the mean (SEM). ****p<0.0005, ***p<0.005.

SEP analyses

The t-test between RHI conditions revealed a significant difference over frontal, central, temporal and parietal channels, with greater amplitude in the asynchronous as compared to the synchronous condition in two time intervals: 140-180 ms (maximal significance at electrode Fc6: $t_{17}=4.74$; $p=0.0002$), coinciding with the latency of the N140 wave; 240-320 ms (maximal significance at electrode C3: $t_{17}=-3.73$; $p=0.002$), coinciding with the latency of the P300 wave. See Fig. 22.

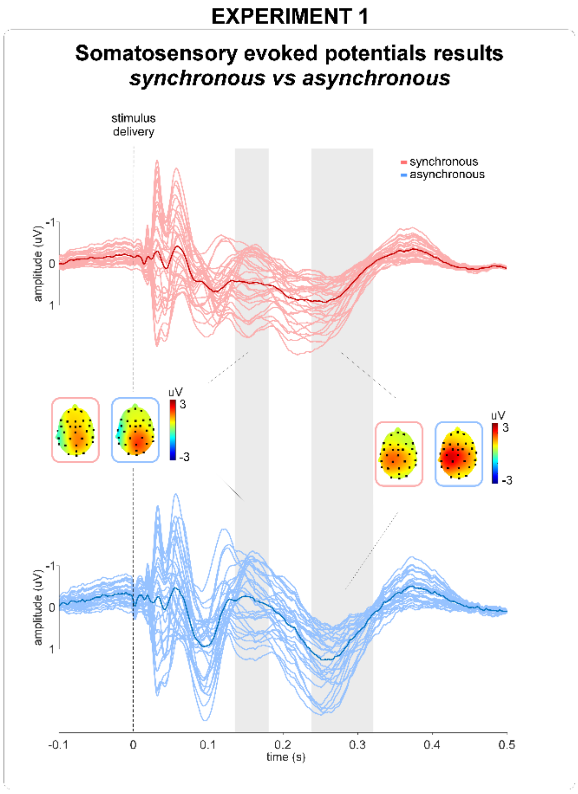

Fig. 22: somatosensory evoked potentials results: comparison between RHI conditions. The butterfly plots represent the grand-average waveforms of synchronous (in pink) and asynchronous (in blue) conditions. Each wave represent a single electrode, the darker wave represent the mean amplitude across electrodes and scalp maps with coloured frames represent the amplitude of the evoked signal across the scalp in the synchronous (framed in pink) and asynchronous (framed in blue) conditions. A t-test comparing RHI conditions is plotted. Significant time intervals are highlighted by grey boxes.

Furthermore, the t-test between the baseline and each RHI condition revealed significant differences only in the baseline vs synchronous comparison, in frontal and central channels. More precisely, we found greater amplitude in the baseline as compared to the synchronous condition within the N140 (maximal significance at electrode F4: $t_{17}=-4.65$; $p=0.0004$) and the P300 (maximal significance at electrode F7: t_{17}=3.51; p=0.003) time-windows. No significant difference emerged between baseline and asynchronous conditions. See Fig. 23.

EXPERIMENT 1

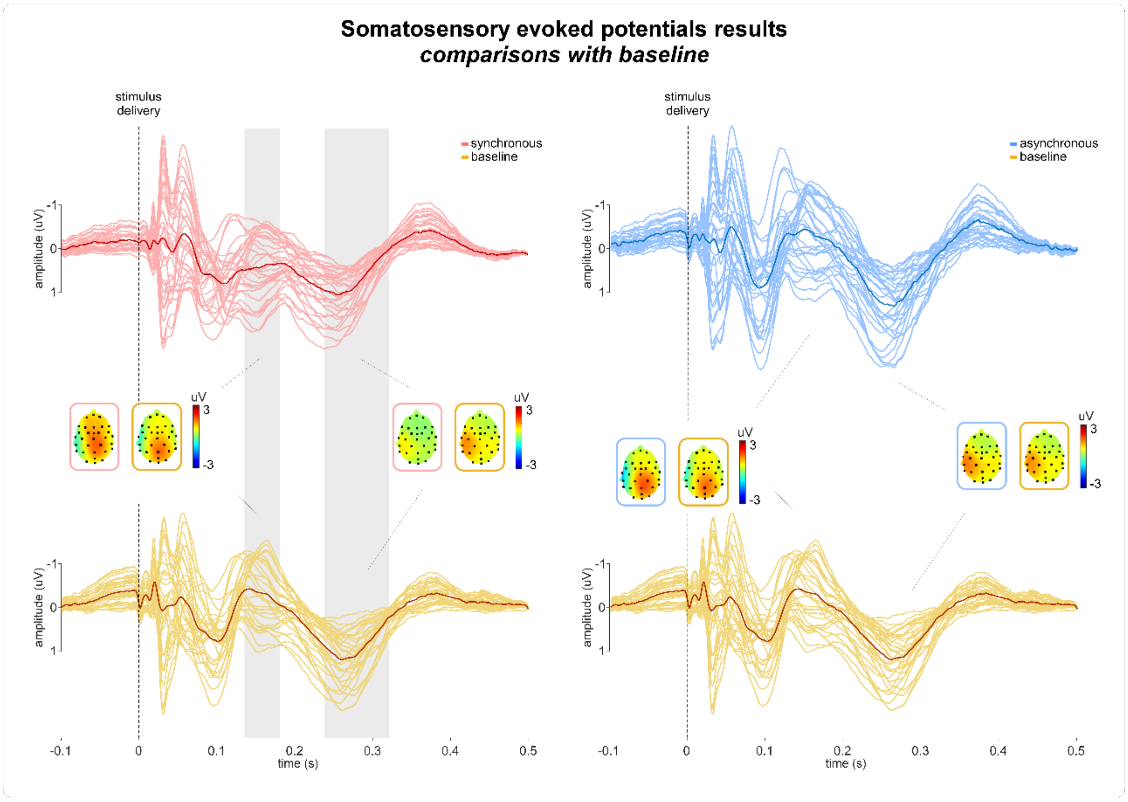

Fig. 23: somatosensory evoked potentials results: comparison with baseline. The butterfly plots represent the grand-average waveforms of synchronous (in pink), asynchronous (in blue) and baseline (in yellow) conditions. Each wave represent a single electrode, the darker wave represent the mean amplitude across electrodes and scalp maps with coloured frames represent the amplitude of the evoked signal across the scalp in the synchronous (framed in pink), asynchronous (framed in blue) and baseline (framed in yellow) conditions. Two t-test comparing each RHI condition with the baseline are plotted (synchronous vs baseline in left panels, asynchronous vs baseline in right panels). Significant time intervals are highlighted by grey boxes.

Correlational analyses

The correlational analyses highlighted a significant positive correlation between the embodiment index and the downregulation index in the N140 component (C4; r=0.71; p=0.001). Furthermore, we also found a positive correlation between the disembodiment index and the downregulation index in the N140 component (C4; r=0.56; p=0.016). See Fig. 24. No significant correlation was found with the P300 component.

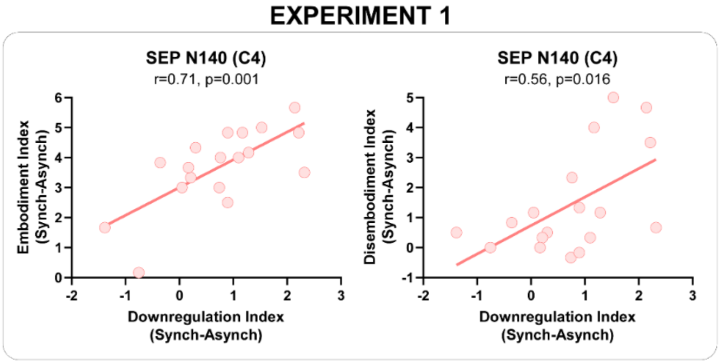

Fig. 24: correlational results of Experiment 1. The figure shows the significant correlations between embodiment index (computed as mean rating attributed to the Embodiment questionnaire in Synchronous-Asynchronous conditions) and the downregulation index (computed as mean amplitude in the N140 time-window in Synchronous-Asynchronous conditions). Note that, since the N140 has a negative polarity, greater amplitude in synchronous vs asynchronous conditions, leading to positive values of the downregulation index, indicated a downregulation effect.

Experiment 2

Behavioural analyses

As in Experiment 1, the Wilcoxon tests revealed a significant difference between condition for both Embodiment (T_{16}=1; Z=3.57; p=0.0004) and Disembodiment (T_{16}=22.5; Z=2.56; p=0.01) questionnaires, with higher values in the synchronous as compared to the asynchronous condition. See Fig. 25.

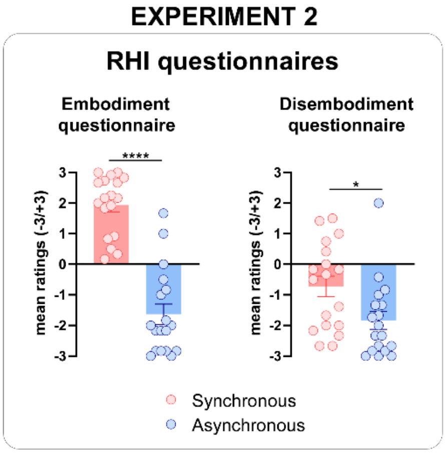

Fig. 25: rubber hand illusion results of Experiment 1. Embodiment Questionnaire results: mean embodiment ratings (Likert Scale − 3/+ 3). Disembodiment Questionnaire results: mean disembodiment ratings (Likert Scale − 3/+ 3). Dots represent each participant’s value, bars represent the standard error of the mean (SEM). ****p<0.0005, *p<0.05.

VEP analyses

The t-test between RHI conditions revealed a significant difference over frontal, central, temporal, parietal and occipital channels, with greater amplitude in the synchronous as compared to the asynchronous condition in a time window between 200 and 310 ms (maximal significance at electrode C3: t_{16}=4.27; p=0.0006), coinciding with the latency of the P3 component. See Fig. 26.

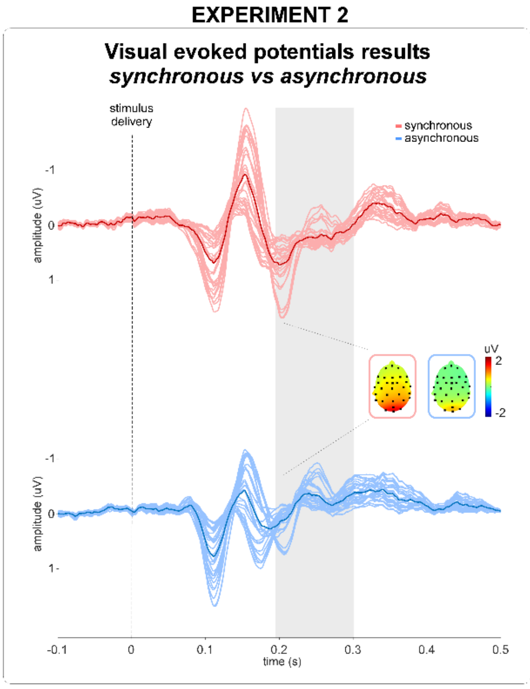

Fig. 26: visual evoked potentials results: comparison between RHI conditions. The butterfly plots represent the grand-average waveforms of synchronous (in pink) and asynchronous (in blue) conditions. Each wave represent a single electrode, the darker wave represent the mean amplitude across electrodes and scalp maps with coloured frames represent the amplitude of the evoked signal across the scalp in the synchronous (framed in pink) and asynchronous (framed in blue) conditions. A t-test comparing RHI conditions is plotted. Significant time intervals are highlighted by grey boxes.

Furthermore, the t-test between the baseline and each RHI condition revealed significant differences for both baseline vs synchronous and baseline vs asynchronous conditions. We found greater amplitude in the synchronous as compared to the baseline condition over frontal, central, parietal and occipital electrodes. More precisely, these differences were observed both in a 150-170 ms time-window (maximal significance at electrode O2: t_{16}=-4.85; p=0.0002), coinciding with the latency of the N3 component and in a 180-220 ms time-window (maximal significance at electrode F8: t_{16}=3.44; p=0.003), corresponding to the latency of the P3 component. See Fig. 27 left panel. Moreover, we found greater amplitude in the asynchronous as compared to the baseline condition over frontal and central channels. This difference was highlighted in a long-latency 290-320 ms time-window (maximal significance at electrode FC5: t_{16}=3.75; p=0.002). See Fig. 27 right panel.

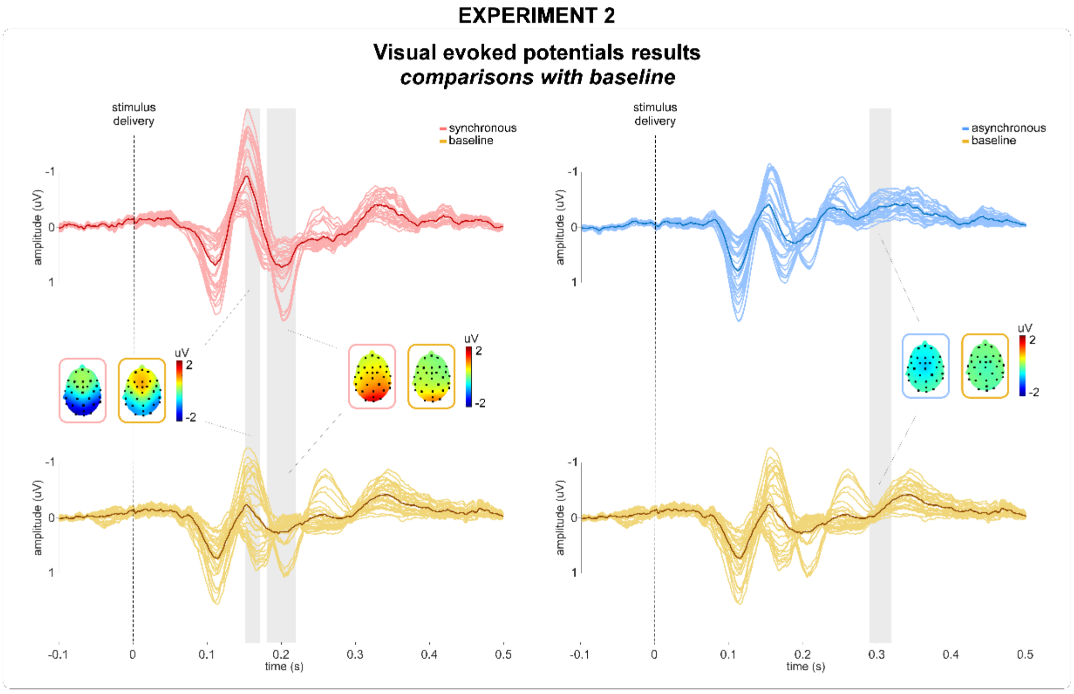

Fig. 27: visual evoked potentials results: comparison with baseline. The butterfly plots represent the grand-average waveforms of synchronous (in pink), asynchronous (in blue) and baseline (in yellow) conditions. Each wave represent a single electrode, the darker wave represent the mean amplitude across electrodes and scalp maps with coloured frames represent the amplitude of the evoked signal across the scalp in the synchronous (framed in pink), asynchronous (framed in blue) and baseline (framed in yellow) conditions. Two t-test comparing each RHI condition with the baseline are plotted (synchronous vs baseline in left panels, asynchronous vs baseline in right panels). Significant time intervals are highlighted by grey boxes.

Correlational analyses

No significant correlation was found.

Discussion

In the present study, we sought to shed light on the neural mechanism that enables embodiment and disembodiment, by measuring the amplitude of somatosensory (SEPs; Experiment 1) and visual (VEPs; Experiment 2) evoked potentials, following either synchronous or asynchronous (control) RHI. Our results compellingly show that, when a rubber hand is incorporated (i.e., during synchronous RHI), the SEPs amplitude following tactile stimulation of the participant's real hand is decreased, whereas the VEPs amplitude following visual stimulation on the rubber hand is increased.

As already mentioned in Study 2.1, previous evidence in favour of a somatosensory downregulation was provided both at the behavioural level, by measuring a tactile perception decrease following the RHI (Folegatti et al., 2009; Rossi Sebastiano et al., 2021; Zopf, Harris, et al., 2011) and at the neural level, by employing non-invasive brain stimulation techniques either to measure the cortical activity during the RHI (Isayama et al., 2019) or to modulate somatosensory activity and measuring the effect on the RHI (Hornburger et al., 2019). In addition, a number of studies has leveraged neuroimaging techniques to investigate the neural correlates of the RHI (Bekrater-Bodmann et al., 2014; Brozzoli et al., 2012; Ehrsson et al., 2004, 2005; Guterstam et al., 2019; Limanowski & Blankenburg, 2015, 2016). Among these, Limanowski and

Blankenburg showed lower touch-related activity in S1 and a significant activity increase in the lateral occipital complex (LOC) and the secondary somatosensory cortex (S2), during the RHI (Limanowski & Blankenburg, 2016). Finally, a series of electrophysiological studies highlighted a decrease in the somatosensory evoked potentials during the RHI (Rao & Kayser, 2017; Sakamoto & Ifuku, 2021; D. Zeller et al., 2015).

Although this body of evidence focused on the somatosensory domain, the evidence concerning the visual domain is sparse. Van Der Hoort and colleagues addressed whether embodiment affects visual awareness in a binocular rivalry paradigm (Hoort et al., 2017). They found that the amount of time in which participants detected a hand image alternating with a mask at 10 Hz increased only when the participants' body ownership over that hand was manipulated. In line with this evidence, in Study 2.1, we showed that visual detection of stimuli occurring around a fake hand is increased when that hand is embodied (Rossi Sebastiano et al., 2021). Furthermore, Longo and colleagues showed that participants who experienced the RHI tended to rate the fake hand as more visually similar to their own hand, as compared to participants who did not experience the RHI (Longo et al., 2009). Although this latter evidence may seem in contrast with the previously mentioned ones, the results are in fact compatible. Indeed, the increase of perceived similarity between own and embodied hands has been interpreted as a detriment of the self/other discrimination ability, resulting from the reupdate of the priors allowing self-recognition, that takes place following the RHI (Apps & Tsakiris, 2014). Conversely, the visual system upregulation during the RHI has been proposed as one of the two concurrent mechanisms through which embodiment is elicited and maintained, and regards the increase of visual perception over the stimuli applied to the fake incorporated hand. To sum up, to our knowledge, only two previous studies addressed the upregulation of visual processing at the behavioural level. Hence, in this study, we described the modulation of both somatosensory and visual neural activity, to provide a comprehensive account of the neural mechanisms underlying the RHI.

Specifically, we chose to employ simple somatosensory and visual stimuli, such as the electrical stimulation of the median nerve and a red LED appearing close to the rubber hand, delivered following a period (12s) of RHI induction. From a methodological point of view, we chose simple somatosensory and visual stimuli to easily characterize the EEG response in terms of latency. Indeed, with more complex and ecological stimuli, such as the tactile stimulation through which the RHI procedure is accomplished [i.e., a series of caresses on the two hands, as in (Zeller et al., 2015; Zeller et al., 2016)], interpreting the effects in terms of latency would have been more difficult. We found an embodiment-dependent downregulation effect in the somatosensory domain in both middle- (N140) and late-latency (P300) SEP components. The correlational analysis revealed that the more the participant experiences embodiment of the rubber hand and disembodiment of the own hand, the more the SEP amplitude results decreased in the N140 component. Interestingly, previous studies have linked tactile awareness processes to the amplitude of the N140 SEP component (Auksztulewicz et al., 2012; Dembski et al., 2021; Schubert et al., 2006). Capitalizing on tactile detection paradigms, these authors showed that the N140 component is the first to reliably differ between detected and undetected stimuli, demonstrating that tactile awareness modulations are reflected at such a latency. The fact that, in our data, the SEP modulation which seems crucial for embodiment and disembodiment mechanisms is localized in the N140 time-window is in line with the behavioural evidence mentioned above, showing that the RHI induces a reduction in tactile perception, measured through detection paradigms (Rossi Sebastiano et al., 2021; Zopf, Harris, et al., 2011). In a similar vein, Aspell and colleagues measured the SEP elicited by a tibial nerve stimulation following the full-body illusion and found that, a middle-latency activation at 110–200 ms was stronger and lasted longer in the asynchronous (control) as compared to the synchronous (illusion) condition (Aspell et al., 2012). They interpreted the effect in terms of an enhancement induced by the detection of asynchrony in the control condition. However, in our view, since they did not include a baseline in their experimental design, they cannot exclude that the effect is in fact due to a reduction of the SEP amplitude in the synchronous condition. Here, the comparisons with the baseline revealed that the N140 and P300 SEP amplitudes were decreased in the synchronous condition while no change was observed in the asynchronous one. Hence, with the present data, we can conclude that the effects observed in the comparison between synchronous and asynchronous condition are due to the downregulation that takes place in the illusion condition.

For what concerns the visual domain, we employed a LED static stimulation to reduce the possible confounds emerging from the use of more complex and ecological stimuli, such as visual touches. Indeed, the processing of more ecological stimuli, such as the visual touches that are applied to the rubber hand during the RHI procedure, entails also the processing of the somatosensory content of the visual stimulus. In other words, by administrating visual touch stimuli, one measures not only the activation of the visual system, but also that of the somatosensory system in response to a seen touch. In this study, we focused on describing the visual system purely, by employing static and simple visual stimuli, in order to investigate whether the visual system was modulated following the RHI and in which direction the possibly observed effect was. However, the fact that we employed such simple and un-ecological stimuli might have reduced the possibility of observing correlations between the embodiment phenomena and the upregulation mechanism. Indeed, while SEPs in Experiment 1 were elicited by tactile stimuli occurring on the participant's hand, thus eliciting the somatosensory network which is involved in the RHI, VEPs in Experiment 2 were elicited by a LED enlightening above the rubber hand, which represents a really different stimulation as compared to the "visual touch" stimulus that are delivered during the RHI.

To our knowledge, the present work represents the very first evidence highlighting an upregulation of the visual processing at the neural level, in line with the predictive coding account. More specifically, our effects were localised in middle-latency time-intervals, with significant increase in VEPs amplitude in the synchronous condition both in N3 (150-170 ms) and P3 (180-220 ms) components. Interestingly, previous studies linked visual perception processes to recurrent feedback activity occurring after 160-200 ms from stimulus onset (Dembski et al., 2021; Fahrenfort et al., 2008; Taylor et al., 2010). Fahrenfort and colleagues recorded EEG while participants were engaged in the detection of masked visual targets. They found that posterior recurrent activity peaking at 160 ms and subsequent alternating pattern of frontoparietal and occipital activity correlated highly with target perception (Fahrenfort et al., 2008). In line with this account, Taylor and colleagues combined TMS and EEG recordings to investigate whether the electrophysiological correlates of conscious phosphene perception were detectable at early or later stages of visual processing. They found that phosphene perception was associated with increased TMS-evoked potentials around 160–200 ms, suggesting that conscious phosphene perception is not an early phenomenon, but rather emerges after extensive recurrent processing (Taylor et al., 2010). Our results indicate embodiment-dependent enhancement of VEPs amplitude in middle-latency components at similar latencies, in line with the previously described enhancement of visual perception of stimuli occurring around an embodied rubber hand (Rossi Sebastiano et al., 2021).

Having determined how the brain balances the afferent inputs in the somatosensory and visual domains, the future direction of this line of research would be to employ more ecological stimulation (i.e., real and visual touches) to investigate how the brain remaps the somatosensory content onto the visual input (see Study 2.3).

Finally, by combining our results with the previous studies described above, we describe the following theoretical model that may account for the RHI. During the RHI procedure, when the fake and the real hands are stroked, somatosensory and visual inputs are processed in the respective primary cortices and then conveyed to parieto-premotor cortices, responsible for multisensory integration (Brozzoli et al., 2012; Casula et al., 2022; Ehrsson et al., 2004, 2005; Gentile et al., 2015; Golaszewski et al., 2021; Limanowski & Blankenburg, 2015; Petkova et al., 2011). According to the predictive coding framework, conflicts emerge when predictions, based on internal models explaining sensory events, do not meet sensory feedbacks, generating a prediction error. Hence, according to this account, the visuo-tactile conflict elicited in the synchronous (illusion) condition of the RHI should be detected by multisensory cortices, thus originating a prediction error. To realign visual and tactile afferences, the brain may implement two strategies, possibly via a top-down modulations operated by high-order cortices on sensory areas (Limanowski & Blankenburg, 2016; Zeller et al., 2016). First, it reduces the weight afforded to somatosensory input originated from the own hand, leading to decreased tactile perception (Rossi Sebastiano et al., 2021; Zopf, Harris, et al., 2011) and somatosensory neural activity (Rao & Kayser, 2017; Sakamoto & Ifuku, 2021; D. Zeller et al., 2015). Second, it enhances the weight afforded to visual input occurring around the fake hand, leading to increased visual perception (Rossi Sebastiano et al., 2021) and visual neural activity (as shown here). Hence, the alteration of the sense of body ownership that takes place in the synchronous RHI might be explained in terms of recurrent feedback projections from multisensory to primary areas, leading to a diametrical modulation of the somatosensory and visual evoked EEG activity in middle- and long-latency components. On the other hand, the asynchronous (control) RHI condition should not generate prediction errors, since tactile and visual stimuli are segregated in time and spatial location. Indeed, the scenario of being touched and, in a separate instance, observing touch onto an external object is not in contrast with common experience. Hence, it should be correctly predicted by internal models, thus, not triggering the neural mechanism responsible for embodiment described above. See Fig. 28.

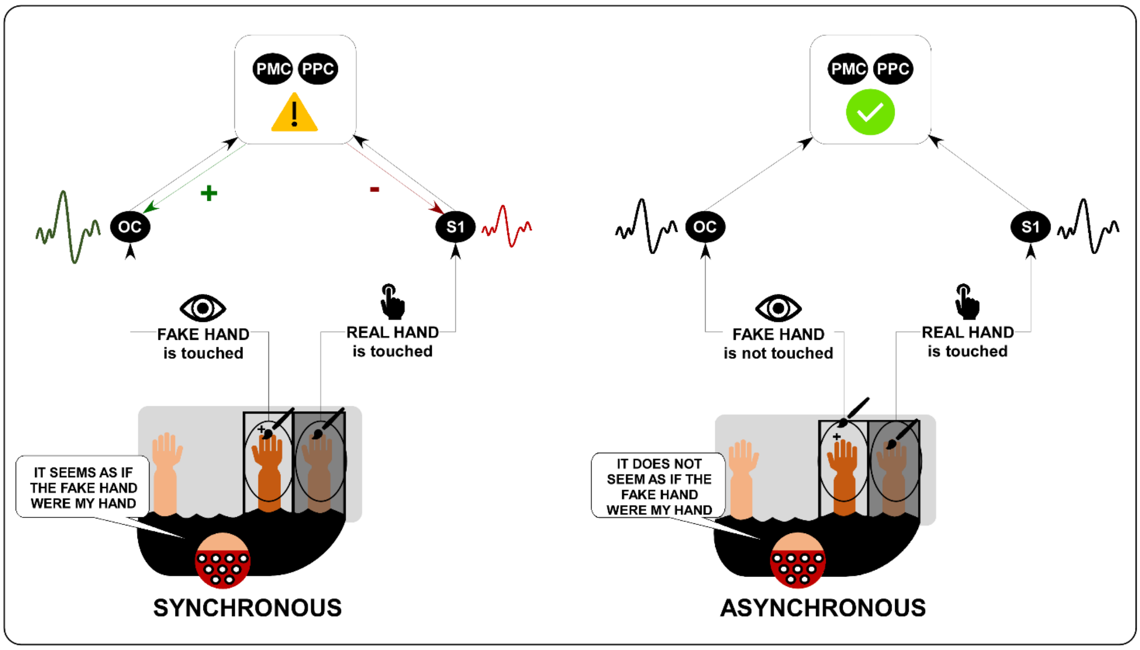

Fig. 28. Neural mechanism allowing the RHI. When touches are applied to both the real and the fake hand in synchrony (left side), the somatosensory and visual inputs are conveyed from primary cortices (OC-occipital early cortices; S1 – primary somatosensory cortices) to higher-order cortices responsible for

multisensory integration. Here, the multisensory conflict is detected, thus generating a prediction error. To explain it away, the multisensory integration cortices downregulate somatosensory processing and upregulate visual processing via feedback projections to the primary areas, leading to the feeling of embodiment of the fake hand. When the touches are applied asynchronously (right side), no incongruency between sensory input is detected, no prediction error emerges and, thus, no feedback modulation is applied, leading to no feeling of embodiment. Note that, here we depicted one of the two possible situations of the asynchronous condition, i.e., those instances when touch occurs on the real hand and not on the fake one. The logic explained here works also for the complementary situation, i.e., those instances when touch occurs on the fake hand and not on the real one.

Conclusion

In conclusion, the present study highlights a diametrical modulation of somatosensory and visual neural activity during the RHI, supporting the results of Study 2.1 at the electrophysiological level. Indeed, during the RHI, we observed two simultaneous processes: the downregulation of the somatosensory system (at a latency consistent with a tactile awareness modulation) and the upregulation of the visual system (at a latency consistent with a visual awareness modulation). We conclude that this neural mechanism is triggered in attempt to restore a stable and coherent body representation, leading to the misattribution of the fake hand to the own body.

Study 2.3: S1 effective connectivity modulation during touch perception and observation through the rubber hand illusion: a TMS-EEG experiment

[This research is currently in preparation as a correspondence for Current Biology, as Pisoni A., Fossataro C., Rossi Sebastiano A., Costantini G., Vallar G., Bolognini N., Romero Lauro L.J., Garbarini F., S1 effective connectivity modulation during touch perception and observation through the rubber hand illusion: a TMS-EEG experiment]

Introduction

In study 2.1 and 2.2 we established the neural mechanism which leads healthy participants to remap the tactile perception onto the visually seen touches, during the RHI. In the present study, we moved the question forward, based on the counterintuitive behaviour that we observed in patients affected by pathological embodiment. Whenever the alien (embodied) hand is touched, these patients report to feel tactile sensations, revealing that the brain might be endowed with the possibility of feeling touches just by seeing what they believe to be their own body being touched. Previous studies investigated the relationship between the sense of touch and the sense of body ownership [i.e., the feeling that body-parts belong to me (Blanke et al., 2015)] by addressing how somatosensory experiences arising from the skin contribute to discriminate the one's own body from the external world. This line of research corroborates the idea that tactile awareness [i.e., the conscious experience of tactile events occurring on my body (Gallace & Spence, 2008)] contributes to the emergence of the sense of body ownership, so that *I believe this body to be mine because I perceive tactile sensations on it*. Here, we investigate the reverse relation from the sense of body ownership to the emergence of tactile awareness. *Do I feel this body perceiving tactile sensation because I believe it to be mine?* In two experiments, we manipulate the sense of body ownership through the RHI in healthy participants and we test whether and how, after a period of illusion induction, the conscious belief about the body gates somatosensory perception of tactile events occurring either on the fake (embodied) hand or on the real (disembodied) hand.

To tackle this issue, following a period of RHI induction, a tactile task of alternating touches on either the real hand (real touch) or the fake one (visual touch) was administered. In the behavioral experiment (Experiment 1), we collected the participants' subjective ratings of tactile perception through a VAS scale. In the neurophysiological experiment (Experiment 2), the neural dynamics (S1 cortical excitability and connectivity following real or visual touches) were investigated by combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG). A TMS pulse was applied over S1, 50 ms following either real touch or visual touch, delivered immediately after the illusion induction. We focused on S1 alpha-band connectivity, as the neurophysiological marker of one's own body somatosensory state (Palva et al., 2005; Pisoni et al., 2018), and in particular on the connectivity between S1 and the parietal operculum, recently described as a fundamental hub for the emergence of tactile awareness (Del Vecchio et al., 2021; Fossataro, Bruno, et al., 2020).

If the sense of body ownership gates tactile awareness, a diametrical modulation of both behavioral and neurophysiological outcomes is expected among conditions. Specifically, during visual-touch trials, when participants observe tactile stimuli applied over the fake hand, higher ratings of (illusory) tactile perception (Experiment 1) and enhanced S1 alpha-band connectivity (Experiment 2) are expected in synchronous (i.e., when participants are expected to report a greater feeling of ownership over the fake hand) as compared to asynchronous condition. Conversely, during real-touch trials, when participants receive tactile stimuli on the real hand, lower rating of tactile perception (Experiment 1) and reduced S1 alpha-band connectivity (Experiment 2) are expected in synchronous (i.e., when participants are expected to report a greater feeling of disownership over the real hand) as compared to asynchronous condition.

Materials and Methods

Participants

Two different samples of fourteen participants (Experiment 1: 10 women, age (mean±sd) = 26.5±0.75, education level = 17±0.28; Experiment 2: 10 women, age = 27.07±4.18, education level = 17.36±1.44) took part in each experiment. The sample size of both behavioral and TMS-

EEG experiments was chosen based on a pilot experiment. G-power software (www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3) was used to estimate, in an the priori analysis, the sample size in a paired t test (two tailed), using the Cohens' d = 1.07; $\alpha = 0.05$; Power (1- β err prob) = 0.98. A total sample size of 14 subjects was indicated. Furthermore, this sample is in agreement with a previous study addressing the RHI dependent modulation of the somatosensory system (Zeller et al., 2014) and a TMS-EEG study investigating the electrophysiological correlates of observed-touch (Pisoni et al., 2018).

Each participant expressed an informed written consent before study procedures, and an Adult Safety Screening Questionnaire (Keel et al., 2000) to assess potential contraindication to TMS, such as neurological, psychiatric, or other relevant medical problems (Rossi et al., 2009) when TMS was applied. The study was performed in the TMS-EEG laboratory of the University of Milano-Bicocca, following the ethical standards of the Declaration of Helsinki. The local Ethics Committee approved the study. All participants were naïve to the purpose of the study.

Rubber Hand Illusion protocol

The RHI was evoked by synchronously stroking the participants' index finger and the fake index finger from knuckle to fingertip, at an approximate frequency of 1 Hz. Asynchronous stroking of the participants' hand and the rubber hand was utilized as a control condition, in which strokes were delivered spatially and temporally in antiphase between the two hands. During the RHI procedure, participants were set in front of a box (7.5×14×10.5 cm) divided into two compartments. The rubber hand was placed on the upper shelf of the box, while the participants' left hand was placed on the lower shelf of the box to conceal it. The rubber hand and the participants' hand were vertically aligned (7.5 cm apart) and congruently positioned with respect to the participants' shoulder. The space between participants' shoulder and the fake arm was covered by a cloth to create the impression that the fake hand was attached to the participants' shoulder. Besides both the participants' hand and the rubber hand there were two human-like plastic hands provided with servomotors allowing them to perform a flexion movement toward a target. This movement generated light touches on the dorsal surface of either the participants' or the rubber hand (Fossataro, Bruno, et al., 2020b). These moving hands were custom-made and fully controlled by an Arduino script (http://www.arduino.cc) (see Fig. 29).

Before starting, participants were familiarized with the setting and instructed to all procedures. As in the classical RHI procedure, participants were firstly blindfolded and asked to indicate the perceived position of their left index finger by pointing with their right index finger toward a vertical ruler attached to the right side of the box. The position marked on the ruler was averaged and referred to as *proprioceptive judgments-pre*. Then, participants were instructed to always maintain their gaze on the fake hand and remain still, while the procedure was performed. In each trial, an experimenter stroked both the participants' and the rubber hand's index fingers for 9 seconds (either synchronously or asynchronously, according to the experimental block). When the stroking period expired, an acoustic signal prompted the experimenter to stop the stroking. After the stroking period three different experimental trials could occur: *real-touch*, wherein the robotic-hand beside the participants' hand touched it; *visual-touch*, wherein the robotic-hand beside the rubber hand touched it; *catch-trials* wherein both implicit and explicit RHI measures were collected. The implicit one consisted of an eye-closed pointing ballistic movement of the right hand towards the aforementioned vertical ruler, signaling the estimated position of one's own hand (the average was referred to as *proprioceptive judgments-catch*). The explicit measure consisted in verbally rating the agreement with an embodiment item (i.e., "I felt as if the rubber hand was my hand") on a Likert scale ranging from -3 to +3 [adapted from (Matthew Botvinick & Cohen, 1998b; Fossataro, Bruno, Giurgola, et al., 2018)]. Note that, in Experiment 1 (behavioural experiment), we collected an additional explicit measure: participants were asked to verbally rate the agreement with a disembodiment item (i.e., "I felt as if my hand was no longer mine") on a Likert scale ranging from -3 to +3 [adapted from (Matthew Botvinick & Cohen, 1998b; Fossataro, Bruno, Giurgola, et al., 2018)]. This measure was not collected in the TMS-EEG experiment because of time constraints, however a subset of participants (N=10) took part in a second session wherein the effectiveness of the procedure in inducing disembodiment was assessed.

Blocks of repeated visuo-tactile stimulations lasting 9 seconds each were employed in this RHI setting, Note that the 9 seconds of visuo-tactile stimulation were used in order to maintain the illusion throughout all the experiment (della Gatta et al., 2016).

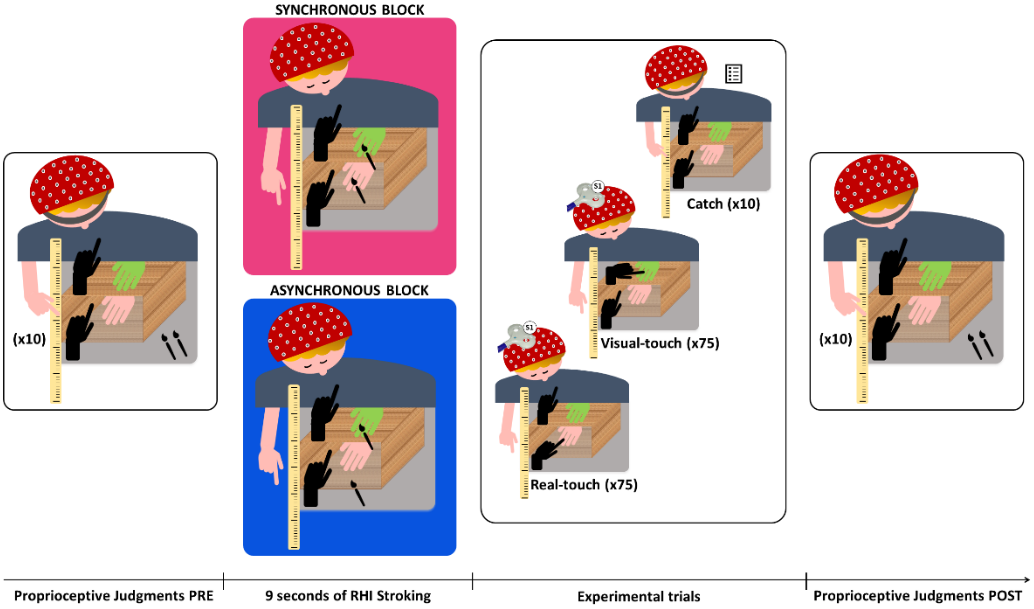

Fig. 29: Experimental procedure. Before and after each block (synchronous in pink and asynchronous in blue), 10 proprioceptive judgements about the own hand position were given by participants (proprioceptive judgement pre and post). During each block, consecutive series of 9 seconds of RHI stroking could be followed by different trials: *real-touch*, wherein the participants' hand was touched; *visual-touch*, wherein the rubber hand was touched; *catch*, wherein a proprioceptive judgment and a subjective rating about the feeling of embodiment and/or disembodiment were collected. In Experiment 1, after real- and visual-touch trials participants gave their tactile perception rating on a 0-20 VAS from "no tactile perception" to "clear tactile perception". In Experiment 2, after real- and visual-touch trials a TMS pulse was delivered over S1 50 ms after the tactile event.

Experiment 1

The behavioral experiment was conducted to test whether the illusory feeling of ownership of the rubber hand affected the participants' tactile perception. The RHI procedure was performed as described above. However, when the moving hand touched the participants' or the rubber hand, participants were asked to rate their feeling of having received a tactile stimulus (i.e., tactile perception rating) on a visual analogue scale (VAS) in which 0 represents "no tactile perception" and 20 “clear tactile perception”. In different sessions, synchronous and asynchronous RHI was performed and 24 trials were collected (20 tactile perception ratings, 4 catch trials), for about 8-10 minutes per session.

Experiment 2

The TMS-EEG experiment was conducted to measure the neural dinamics underpinning the tactile perception modulation that takes place the RHI. TMS-EEG was applied during the ad-hoc RHI protocol employed in the described above experiment, with two stroking blocks collected separately. In each block, a total of 160 trials were collected and each trial consisted of a stroking period lasting 9 s immediately followed by the three different experimental trials (75 real-touch, 75 visual-touch and 10 catch-trials). When the moving hand touched the participants' or the rubber hand, a signal was prompted through a touch controlling device (Makey Makey) triggering a TMS pulse over the participants' right S1 hand area 50 ms after the tactile stimulus delivery (see Fig. 29). This SOAs was chosen according to previous TMS-EEG evidence highlighting a different S1 response, in terms of EEG functional connectivity, at this latency following perceived and observed tactile events (Pisoni et al., 2018). In catch-trials, the TMS pulse was not delivered and implicit and explicit RHI measures were collected. The inter-trial interval was jittering between 100-500 ms for a total duration of ~12.6-13s for each trial (catch trials 19.6-20 s). Each block lasted approximately 35 min, for a total experimental time of 70 min. Also in this case, the participant's hand was kept in place across the experimental blocks.

TMS stimulation

TMS was delivered using an Eximia™ TMS stimulator (Nexstim™, Helsinki, Finland) with a biphasic focal figure-of-eight 70-mm coil. As stimulation target, the right S1 hand area was chosen, following the MNI coordinates 47, -32, 59 (Boakye et al., 2000) as in previous TMS and TMS-EEG studies targeting this region (Pisoni et al., 2018). These coordinates were localized on normalized individual MRIs: after the acquisition of a high-resolution (1x1x1 mm) structural magnetic resonance image (MRI) using a 3T Intera Philips body scanner (Philips Medical Systems, Best, NL), the images were normalized in SPM 12, and the MNI coordinates were localized on these images. This information was then used to perform the neuronavigation on the individual MRIs through an integrated Navigated Brain Stimulation (NBS) system (Nexstim™, Helsinki, Finland). This system uses an infrared-based frameless stereotaxy technique to map the subject's head and coil position within the reference space of the individual's MRI. With this NBS system it was also possible to track online, during the stimulation, the coil's position and orientation, ensuring the reproducibility of the stimulation protocol across sessions. Furthermore, the NBS system estimated the intensity (V/m) of the intracranial electric field induced by TMS at the stimulation hotspot, considering both individual head and brain shapes, as well as the distance from the scalp and the position of the coil. To determine stimulation intensity, we adopted a functional procedure setting the stimulator output according to the recorded TMS evoked response. Specifically, we chose an intensity that elicited a cortical response of at least 6μV. The mean estimated electric field at the stimulation target was 98.6 V/m (SD ± 10.6), corresponding to a mean stimulation intensity expressed as a percentage of the maximal stimulator output (MSO) of 59.6% (SD ± 2.6). Within each subject, the MSO intensity was kept fixed across TMS-EEG recordings. The coil was placed tangentially to the scalp, and no MEPs of the contralateral upper limbs were reported for any subject.

Data analysis

RHI measures (Experiment 1&2)

In all experiments, the Proprioceptive Drift was calculated as the difference between the proprioceptive judgement collected before the RHI procedure (proprioceptive-judgment pre) and both the proprioceptive judgement collected after the RHI (proprioceptive-judgment post) and the proprioceptive judgement collected during the catch trials (proprioceptive-judgment catch). The obtained value was taken as a measure of proprioceptive relocation (i.e., proprioceptive shift toward the rubber hand) and entered in a 2x2 repeated measures ANOVA with block (2 levels: synchronous; asynchronous) and time (2 levels: catch; post) as within subject factors. Post-hoc comparisons were performed by means of Bonferroni test. The ratings to the embodiment and/or disembodiment item were analyzed by means of a paired T-test (2 tailed). All analyses has been performed by means of Statistica software 7.

Experiment 1

Tactile perception ratings

In the behavioral experiment, the tactile perception ratings were entered in a 2x2 ANOVA with block (2 levels: synchronous; asynchronous) and condition (2 levels: Real-touch; Visual-touch) as within subject factors. Planned comparisons between synchronous and asynchronous conditions in real and visual touch conditions were performed for post-hoc analyses.

Experiment 2

EEG data recording and analysis

For each participant, two TMS-EEG recordings of 160 pulses each were performed. EEG signal was continuously acquired using a TMS compatible 60-channels amplifier (Nexstim Ltd., Helsinki, Finland). A proprietary sample-and-hold circuit held the amplifier output constant from 100µs pre to 2ms post-TMS pulse, (Virtanen et al., 1999). The ground was represented by two electrodes over the subject's forehead, while electrooculogram (EOG) was recorded by two electrodes placed near the eyes. TMS noise was masked by continuously playing an audio track created by shuffling TMS discharge noise (Casarotto et al., 2010; Massimini et al., 2005; Pisoni et al., 2017; Romero Lauro et al., 2014), preventing the emergence of auditory evoked potentials linked to the coil click (ter Braack et al., 2015). Electrodes' impedance was kept below 5 kΩ, and EEG sampling rate was 1450 Hz.

Data pre-processing was performed using Matlab R2012a (Mathworks, Natick, MA, USA). First, a band-pass filter between 1 and 45 Hz was applied. Second, EEG signal was split in epochs 800 ms before and 800 ms after TMS pulse, down-sampling EEG signals to 725 Hz. Third, artifact rejection was performed by removing trials with excessive artifacts by visual inspection (Casali et al., 2010), and TEPs were computed by averaging selected artifact-free single epochs. The spherical interpolation function in EEGLAB (Delorme & Makeig, 2004) was used to interpolate bad channels. TEPs were then average-referenced and baseline corrected between -800 ms and -

650 ms before TMS pulse, and finally, to remove remaining muscular, ocular, or magnetic artifacts, an Independent component analysis (ICA) was applied.

Data analysis was performed using the FieldTrip Matlab toolbox (Oostenveld et al., 2011).

TEPs amplitude. A first analysis was performed on TEPs amplitude by comparing responses to real- and visual-touch trials in Synchronous or Asynchronous RHI conditions using a whole-head cluster-based permutation comparison, a procedure correcting multiple comparisons by permuting the data and clustering them based on their spatial and temporal proximity. The cluster-corrected threshold is obtained by computing the permutation distribution of the maximum cluster statistic [for a thorough description of this approach see (Maris & Oostenveld, 2007)]. For these comparisons, 10000 permutations were performed for the whole 0-400 ms time window with a permutation-significant level of p=.05. Critically, four comparisons were performed, testing differences between real- vs. visual-touch within each of the two RHI protocols (Synchronous and Asynchronous) and vice-versa. Second, to explore the potential interaction between touch type and RHI condition, the same analysis was run on TEPs differences between real- vs. visual-touch in Synchronous and Asynchronous conditions, and vice-versa, as this is the suggested methods to perform a 2x2 interaction analysis in Fieldtrip (Oostenveld et al., 2011).

Alpha-band connectivity. Concerning the functional connectivity analysis, this was computed at the source level. The forward model was created starting from a Boundary Element Model (BEM) obtained segmenting a subject MRI into five standard tissues (Gray and white matters, CSF, Skull and Scalp). The head model was then computed assigning standard conductivity values for the scalp, skull and brain compartments (Fuchs et al., 2002; Vorwerk et al., 2014). Source space was defined performing a cortical reconstruction and volumetric segmentation of the grey matter with the Freesurfer image analysis suite (Fischl, 2012), down sampled to 8193 cortical sources and re-aligned to the head model space. Finally, individual lead field matrices were computed by aligning this forward model with the individual electrodes' positions, which were recorded during each TMS-EEG session. This model was also used to compute the spatial filter matrix, i.e., the inverse of the lead field matrix. Source reconstruction of the EEG time-series was conducted with the LCMV method implemented in Fieldtrip toolbox (Mahjoory et al., 2017; Popov et al., 2018; Van Veen et al., 1997) for solving the inverse modeling. Source signals were then segmented in 89 regions of interest (ROIs) according to the AAL brain atlas (Tzourio-Mazoyer et al., 2002). The computed source time-series were then averaged to index each ROI source activation (Hillebrand et al., 2012). Functional connectivity was performed for right S1 source space-time series. Specifically, *Phase Locking Value* [*PLV*, (Hirvonen & Palva, 2016; Lachaux et al., 1999)] was computed between S1 and the other brain parcels for the α band (8-12Hz) for each of the four experimental conditions, since this is the frequency of interest in discriminating somatosensory processing conditions and visual-real touch differences (Hirvonen & Palva, 2016; Pisoni et al., 2018). This analysis was also performed on surrogate datasets created by shuffling the phase of the source reconstructed time series for each experimental condition and considered EEG band. To reduce the risk that spurious connectivity could be included in our results, real data were compared with the surrogate computing a t-test performed on each connectivity pair (88, right S1 with the other 88 brain parcels), and corrected for multiple comparison based on 2000 permutation approach, implemented in Matlab, with a significance level of p= 0.05 (Pisoni et al., 2018). Surviving connections were then plotted to highlight the resulting functional connectivity between the right S1 and the rest of the brain parcels. We ran two analyses on these data. First, to compare the resulting global connectivity patterns across experimental conditions, the *network strength* was computed as the sum of the PLV of the resulting connections. Second, we specifically tested whether the alpha-band connectivity between S1 and the Parietal Operculum (PO), which has been demonstrated as a crucial node for tactile awareness (Del Vecchio et al., 2021; Fossataro, Bruno, et al., 2020b), differed across conditions by comparing the PLV value of such connectivity across experimental conditions. In both cases we performed the very same analysis, employing the statistical programing environment R (R Development Core Team, 2014). Linear mixed effects models were used as the main statistical procedure (Baayen et al., 2008). Dependent variables (i.e., network strength or S1-PO PLV) were submitted to a series of linear mixed effects regression using LMER procedure in "lme4" R package [version 1.1–5; (Bates, 2015)]. A series of likelihood ratio tests was used to assess the inclusion of fixed effects that significantly increased the model's goodness of fit by means of a forward stepwise inclusion procedure. As fixed effects, condition (factorial, 2 levels: visual-touch vs real-touch), block (factorial, 2 levels: synchronous vs asynchronous), and their interactions were tested. Concerning the random effect structure, a by-subject random intercept was included. We report the parameters of the final best fitting models with significance levels based on Satterthwaite's degrees of freedom approximation in "lmerTest" R package (version 2.0–29). Moreover, to directly contrast single levels of the significant interactions and main effects, post hoc procedures were carried out on the best fitting final model with the "phia" R package (version 0.2-0), applying Bonferroni-Holmes correction for multiple comparisons. Note that, while network strength was computed in the whole brain so a single analysis was performed, for the PLV analysis we ran two analysis, one for each hemisphere.

Results

RHI analyses (Experiment 1 & 2)

In both Experiments, as expected, the illusory experience during the RHI was greater in synchronous than asynchronous blocks, as assessed through subjective (Experiment 1 embodiment: T=7.63, $p<0.0001$; disembodiment: T=3.87, p=0.002; Experiment 2 embodiment: T=7.38, $p<0.0001$; disembodiment_10subjects: T=3.67, p=0.02) and objective [Experiment 1 proprioceptive drift (main effect of condition): $F_{1,13}=10.3$, p=0.007; Experiment 2 proprioceptive drift (main effect of condition): $F_{1,13}=5.3$, p=0.039) measures (Longo et al., 2008; Tsakiris & Haggard, 2005).

Experiment 1

Tactile perception ratings

The ANOVA revealed a significant interaction between block and condition ($F_{1,13}=18.73$, p=0.0008; see Fig. 30), with significantly enhanced tactile perception in the synchronous as compared to the asynchronous condition in visual-touch trials (p=0.0004), and, complementarily, significantly reduced tactile perception in the synchronous as compared to the asynchronous condition in real-touch trials (p=0.03).

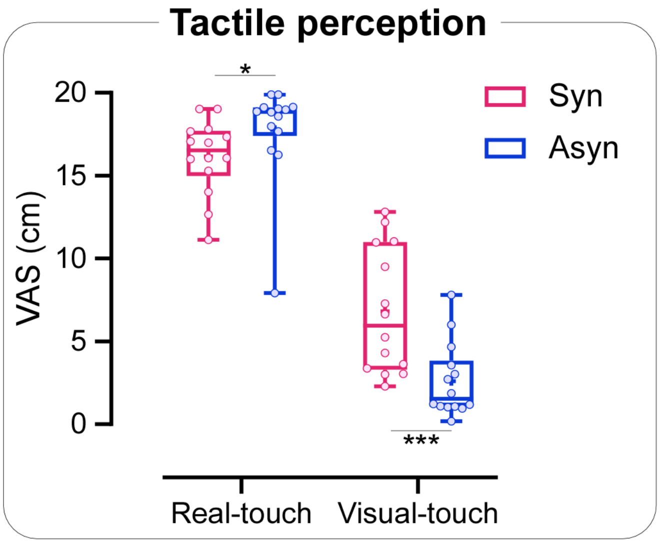

Fig. 30. Tactile perception ratings (VAS scale) in real- and visual-touch conditions are depicted both in synchronous (pink) and asynchronous (blue) blocks. Higher values indicate a stronger tactile perception. In the boxplots, the whiskers represent the minimum and the maximum value, the limits of the box represent the first and the third quartile, the median is depicted by the line that divides the box into two parts, and the cross represents the mean. Dots represent individual participants. Asterisk indicates significant comparisons (*P < .05; ***P < .0005).

Experiment 2

<u>EEG data recording and analysis</u>

TEPs amplitude. In real-touch conditions, for both synchronous and asynchronous RHI protocols, a first negative component arises around 20 ms, peaking over the centro parietal right electrodes, and is then followed by a longer and more complex component peaking around 50 ms, with a positive topography overlapping the same regions. Finally, late components are visible around 100 and 200 ms post TMS, the former peaking over more posterior right regions and the latter moving to the parietal left area (See Fig. 31, upper row). Similarly, visual-touch condition showed components peaking around the same time-windows, but with relatively lower amplitude (Fig. 31, middle row), as previously reported (Pisoni et al., 2018). This observation is confirmed by the cluster-based analysis, which indicated a greater activity for real-touch compared to visual-touch synchronous trials in a negative cluster between 10 and 70 ms (p=0.018), with significant differences over the central (20 ms) and left parietal (50 ms) electrodes (Fig. 31, bottom row). Furthermore, a second negative cluster resulted significant between 80 ms and 150 ms (p=0.046), peaking at 100 ms over the right parieto-occipital electrodes. Finally, a positive cluster resulted significant between 160 ms and 250 ms (p<0.001), with greater activity in the real- as compared to the visual-touch condition over a bilateral central region (Fig. 31, bottom row). Concerning the asynchronous RHI blocks, a greater number of clusters resulted significant in the comparison between real and visual-touch conditions. Negative and positive clusters significantly differed in the early TEP components. A first cluster, with a greater negative activity in the real- compared to the visual-touch condition, was significant between 10 and 70 ms post TMS (p=0.006), peaking over the central frontal regions (20 ms), moving to left temporal areas (50 ms). A positive cluster concurrently resulted significant between 15 and 75 ms (p=0.035), with greater activity in Self touch condition over the right temporo-occipital regions (25 ms) and to the central frontal area (50 ms). Similarly, positive and negative clusters resulted significant between 80 ms and 140 ms (p=0.026 and p=0.019 respectively), peaking over centro-frontal and centro-parietal regions at 100 ms latency. Finally, both positive and negative clusters significantly differed between experimental conditions from 160 ms and 260 ms post TMS (p<0.001 and p=0.03 respectively). In this case, greater activity for the real-touch condition was reported over bilateral parietal regions and central frontal areas.

These results highlight an overall greater S1 activity after perceived touch compared to observed touch, as previously reported (Pisoni et al., 2018). Conversely, comparing real-touch trials in synchronous vs. asynchronous RHI conditions did not result in significant differences, as well as comparing visual-touch trials across RHI procedures. Similarly, no significant difference was reported for the 2x2 (touch type by RHI condition) interaction analysis.

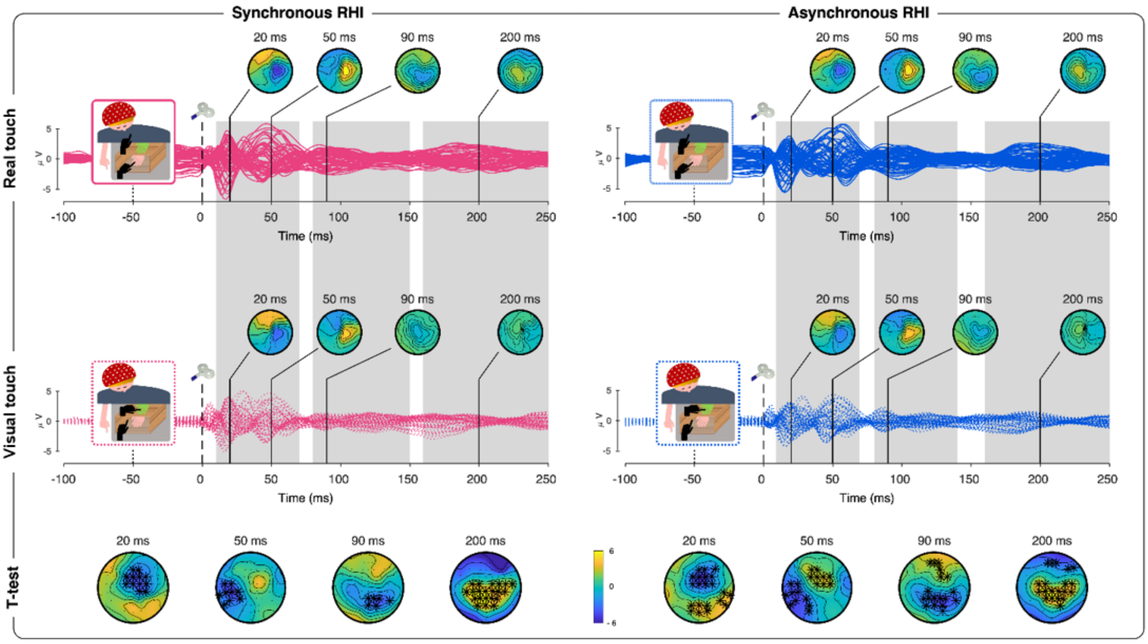

Fig. 31. TEPs amplitude results. In the upper rows, TEPs waveforms from the 60 EEG channels in the four experimental conditions are reported. Solid lines indicate real-touch conditions, while dotted lines indicate visual-touch conditions. Pink lines indicate synchronous RHI, blue lines indicate asynchronous RHI. In the bottom row,

Alpha-band connectivity. In the asynchronous RHI condition we found that TMS delivered over S1 at 50 ms after the real-touch onset elicited a remarkable functional network, encompassing bilateral temporal and parietal areas, as well as occipital regions. Conversely, observing the touch delivered over the rubber hand triggered a functional network encompassing the contralateral frontal and temporal regions only (see Fig. 32, real- and visual-touch in left panels). In the synchronous RHI condition, instead, real-touch trials showed a reduced connectivity in the α-band compared to the asynchronous condition, decreasing the connections in the occipital regions but keeping a vast network in the bilateral frontal and temporal areas. The visual-touch trials, instead, increased their connections compared to the asynchronous RHI protocols, mainly showing additional connections in the right hemisphere with occipital, temporal and frontal regions (see Fig. 32, real- and visual-touch in right panels).

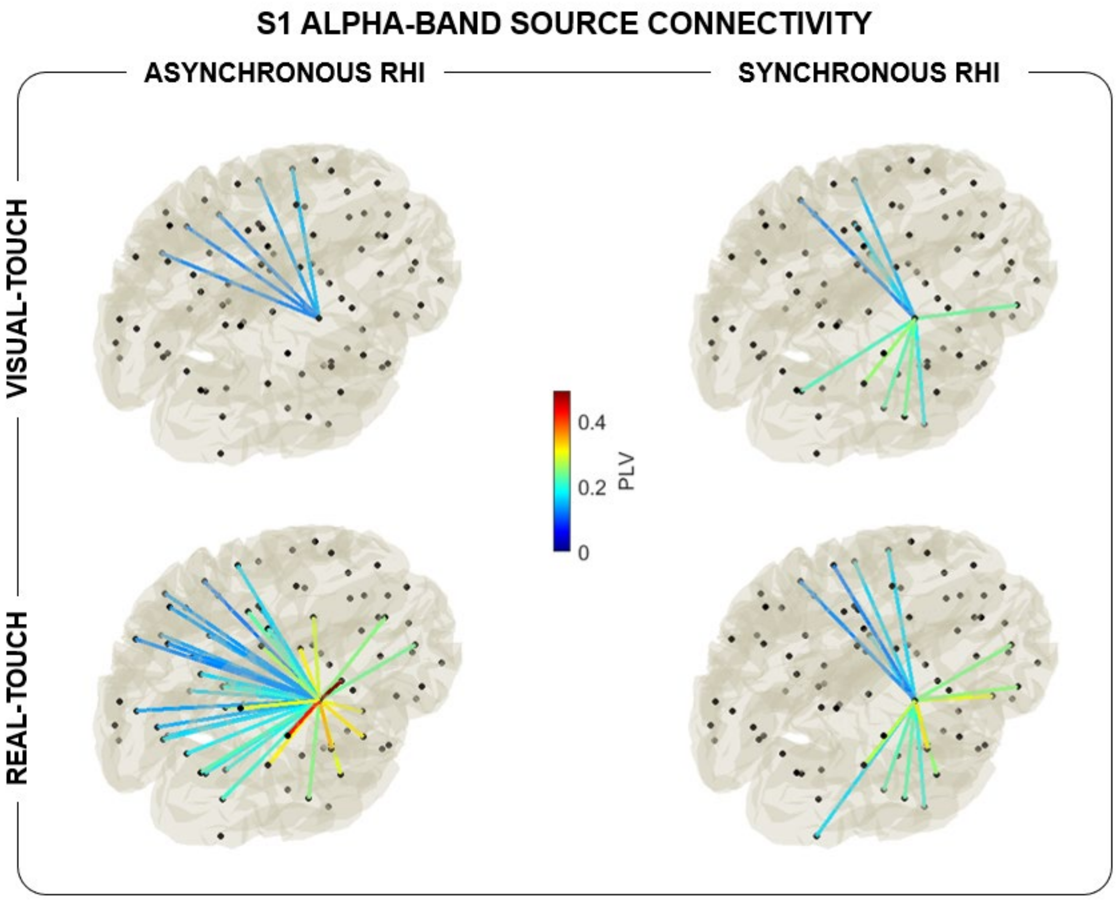

Fig. 32: Source connectivity alpha-band S1 to other areas. In the figure, the PLV at the source level between S1 and the other brain parcels in the 400ms post-TMS time windows is shown. PLV was employed to estimate S1 functional connectivity during real- and visual-touch in synchronous and asynchronous RHI blocks.

The final model on *network strength* included as fixed effects the main effects of condition (b= 10.1; t_{39}= 13.4; p<0.001) and condition × block interactions (b= -9.3; t_{39}= -8.7; p<0.001; see Fig. 33), while no significant main effect of block (b= 1.43; t_{39}= 1.9; p= 0.06) was found. Postdoc comparison showed that the interaction was explained by a diametrical pattern between visual- and real-touch conditions in synchronous and asynchronous RHI blocks. Crucial for the aim of the present study, we found not only that network strength was significantly reduced in synchronous as compared to asynchronous RHI for real-touch conditions (p<0.001), but also that there was a trend for significance for an increase in synchronous as compared to asynchronous RHI for visual-touch conditions (p=0.057). Moreover, while real- and visual-touch conditions differed in the asynchronous (control) block ($p<0.001$), there was no difference in the synchronous one ($p=0.3$).

Similar results were found only in the left (and not in the right) hemisphere, concerning the specific analysis conducted on the connectivity between S1 and PO. The final model on *PLV* included as fixed effects the main effects of condition ($b= 0.05$; $t_{39}= 2.97$; $p=0.005$) and condition × block interactions ($b= -0.06$; $t_{39}= -2.63$; $p=0.01$), while no significant main effect of block ($b=0.03$; $t_{39}= 1.9$; $p= 0.07$) was found. Postdoc comparison showed that, while real- and visua-touch conditions differed in the asynchronous (control) block ($p<0.006$), there was no difference in the synchronous one ($p=0.46$).

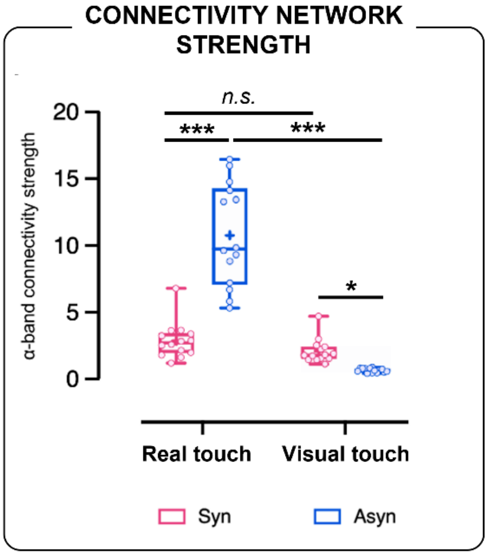

Fig. 32: Connectivity network strength results. Statistical comparisons among conditions were run on the sum of the PLV of the resulting connections (i.e., network strength). Here, connectivity strength in real and visual touch conditions is shown for both synchronous (pink) and asynchronous (blue) blocks (condition × block interaction).

Discussion

In the present study we investigated the relationship between the sense of body ownership and tactile perception, both at the behavioural and neural level. We manipulated the sense of body ownership by applying the RHI, which successfully induced embodiment and disembodiment only in the synchronous (experimental) and not in the asynchronous (control) conditions.

Furthermore, we employed a tactile task in which either subjective report of tactile perception (Experiment 1) or alpha-band connectivity network (Experiment 2) were measured following either a real touch (i.e., a touch occurring to the participant's real hand) or a visual touch (i.e., a touch delivered on the rubber hand). Interestingly, in both experiments, diametrical results of the tactile task were found, depending on whether tactile events, delivered after the illusion induction, occurred on either the fake or the real hand. In Experiment 1, a touch delivery on the incorporated hand (visual-touch) induced significantly increased tactile perception ratings, while a touch delivered on the disincorporated real hand (real-touch) evoked significantly lower tactile perception ratings. Thus, from a behavioral point of view, we demonstrated that the embodiment of the rubber hand gates tactile perception, fostering the explicit tactile sensations of events occurring onto the fake (embodied) hand to the detriment of that occurring onto the real (disembodied) hand.

As concerns TEPs results, we found significant differences between real- and visual-touch conditions, with the former eliciting greater responses as compared to the latter. Conversely, this analysis did not reveal any difference between RHI synchronous and asynchronous blocks. However, functional connectivity results show that, soon after the illusion induction (i.e., after synchronous as compared to asynchronous condition), there is a reduction of S1 alpha-band connectivity for real-touch and concurrently an increase of S1 alpha-band connectivity for visual-touch. In line with previous findings (Palva et al., 2005; Pisoni et al., 2018), real-touch elicited a remarkable functional network, encompassing bilateral temporal and parietal areas, as well as occipital regions, throughout the asynchronous control block. The disembodiment of the own hand induced in the synchronous block strongly reduced this functional network, decreasing connections in the occipital and parietal regions with the contralateral hemisphere while in the ipsilateral hemisphere the connections with M1 and IPL were lost. This is in agreement with the idea that the drop in the hand-motor network accompanies the disembodiment of the real hand during the RHI experience (Casula et al., 2022; della Gatta et al., 2016; Isayama et al., 2019). Conversely, visual-touch following the asynchronous (control) block triggered a narrow functional network encompassing the contralateral frontal and temporal regions only. Crucially, the sight of the embodied rubber hand being touched significantly enhanced such a functional network, showing additional connections with occipital, temporal and frontal regions in the ipsilateral hemisphere. As far as the specific alpha band connectivity between S1 and PO is concerned, visual- and real-touch elicited a similar functional connectivity network only when the fake hand was incorporated, in the hemisphere contralateral to the hand subjected to the illusion. This result indicates that, when the hand is embodied, S1 and PO are connected as if the real hand was being touched. Previous evidence from intracortical EEG show that long-lasting tonic responses to tactile stimuli recorded in PO represent the neural substrate of somatosensory awareness (Avanzini et al., 2016). Furthermore, we previously showed that tonic responses in PO are enhanced by concomitant visual stimuli (Del Vecchio et al., 2021), paralleling the effectiveness of visuotactile stimuli in ameliorating tactile awareness deficits in stroke patients (Fossataro, Bruno, et al., 2020). This evidence supports the idea that the belief of owning the stimulated body part induces to experience tactile sensations on it, also revealing that the brain is endowed with the inner potentiality of sensing a 'visual touch'. Our results are in line with previous electrophysiological data in monkeys, showing that, following a period wherein touches occurred on a virtually displayed arm synchronously with physical brushes of the monkeys' arm, neurons in S1 started to respond to visual touches applied alone on the virtual arm (Shokur et al., 2013).

Finally, an issue that needs to be discussed is the absence of a TEPs modulation between RHI blocks. Indeed, at first glance, this result might seem in contrast with the results of Study 2.2, showing a diametrical modulation of somatosensory and visual responses during the RHI. However, since in study 2.3 we tested S1 activation following a period of RHI induction and either a visual- or a real-touch, here, only the somatosensory (and not the visual) system was investigated. From the results of Experiment 1 of study 2.2 (i.e., the experiment investigating the somatosensory system), one could have expected to observe a reduction of TEPs amplitude in synchronous as compared to asynchronous blocks in real-touch conditions. We believe that the reason underpinning this negative result might be twofold. First, from a methodological point of view, the experimental design was conceived so that, while synchronous and asynchronous blocks were performed in different days, within the same session real- and visual-touch conditions alternated, making it more likely to observe a real- vs visual-touch difference rather than a between-RHI-blocks one. Second, from a conceptual point of view, studies 2.2 and 2.3 seem indeed to have highlighted consistent results. In study 2.2, we found a downregulation of SEPs at long latency timings, which follows the latency of early components that have been linked to S1 activation. As discussed in study 2.2, the timing of this effect is indeed consistent with a modulation of the recurrent activity between high-order associative cortices and S1 (Auksztulewicz et al., 2012; Dembski et al., 2021; Schubert et al., 2006). Hence, from our point of view, it makes sense that, in study 2.3, we did not observe a modulation of S1 activity itself (TEPs results), but rather a modulation of the connectivity between S1 and high-order areas, such as the parietal operculum.

Taken together, we believe that our data provide evidence for a top-down body ownership dependent modulation of tactile awareness and its electrophysiological signature in humans, supporting the view that '*I feel a body perceiving tactile sensation because I believe it to be mine'*.

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General conclusions

The present thesis aimed to shed light on the relationship between the sense of body ownership and sensorimotor perception, capitalizing on two complementary strategies, i.e., the study of body ownership disturbances induced either by a brain damage or by experimental manipulations.

The study of neurological patients has allowed us to describe double dissociations between pathological embodiment and both motor [e.g., see (Rossi Sebastiano, Poles, et al., 2022)] and sensory [e.g., see (Fossataro et al., 2016; Fossataro, Bruno, et al., 2020b)] deficits. If one's own body representations can be present in the brain even when motor and sensory domains have been damaged by a brain lesion and body ownership disturbance does not automatically entail sensory and motor deficits (Garbarini et al., 2020; Pia et al., 2020), one can deduce that the sense of body ownership and both sensorimotor functions are rather independent one from the other. Hence, neuropsychological evidence has allowed to rule out the idea that bodily self-awareness emerges as a mere "collection of perceptions" (Hume, 1978; Penelhum, 2000; Strawson, 2011). However, the fact that body ownership and sensorimotor functions are not necessarily co-present does not exclude the possibility that one exerts a top-down modulation on the other ones. In other words, the fact that self-awareness is not a mere collection of perceptions does not necessarily mean that it is an abstract representation which has no relationship with bodily sensations and actions (Black, 2008; Kaukua & Kukkonen, 2007; Matthews & McKenna, 2002). More specifically, our hypothesis was that when we act with and perceive on our body segments, the belief of owning that body-part plays a crucial role in planning the movement or perceiving the sensation. Hence, in a series of studies, we addressed whether the sense of body ownership exerts a top-down modulation on both motor control and sensory perception.

In Chapter 2, two studies concerning the motor domain are discussed, wherein we pinpoint that body ownership exerts a top-down modulation on motor control. In *Study 1.1* we capitalized on pathological embodiment to show that, when an alien hand is incorporated, movements are planned from the alien hand position, and not from the own hand's physical location (Rossi

Sebastiano, Poles, et al., 2022). *In Study 1.2* we exploited the RHI in human and non-human primates to demonstrate that, if the own hand is the target of a self-directed movement, we aim toward the alien hand when the latter is incorporated (Errante et al., *in preparation*). More generally, these studies provide evidence that when our body is either the agent or the target of an action, the movement is calibrated on the basis of *the position of the hand which is believed to be one's own* and *not the own hand's physical location*.

In Chapter 3, three studies concerning the sensory domain are discussed, wherein we pinpoint that body ownership exerts a top-down modulation on the sensory systems, gating tactile perception both at the behavioural and at the neural level. In *Study 2.1* we show, at the behavioural level, that somatosensory and visual systems are diametrically modulated in order for the RHI to take place (Rossi Sebastiano et al., 2021), in line with the predictive coding framework (Apps & Tsakiris, 2014; Karl Friston & Kiebel, 2009; Limanowski & Blankenburg, 2013). The up-weighing of visual information (i.e., the rubber hand is being touched) as well as the down-weighing of somatosensory information (i.e., my hand is being touched), leads to the shift of the tactile sensation from the physically own hand to the incorporated alien hand (i.e., I feel touch on the rubber hand, hence the rubber hand is my own). These behavioural results were further confirmed in *Study 2.2*, in which we provide electrophysiological evidence of such a mechanism, conclusively establishing the neural dynamics underpinning the emergence of the RHI (Rossi Sebastiano et al., *in preparation*). Finally, in *Study 2.3* we moved the question further, shedding light on the neural mechanism that allows our brain to feel tactile sensations when an alien (embodied) hand is touched (i.e., visual touch), also reducing tactile perception on the own (disembodied) hand (Pisoni et al., *in preparation*). More generally, these studies demonstrate that sensory perception is shaped by the belief of owning a body part.

Altogether, this thesis provide evidence that, when we move a body part or perceive on it, the experience is not confined within the boundaries of *what physically belongs to the own body*, but rather it pertains to *the body parts that are believed to be one's own*. In other words, if someone's body ownership is modulated so that they believe that an alien hand belongs to the own body, they “move and perceive” from the alien hand (i.e., the one which is believed to be one’s own) and not from the own hand (i.e., the one which is physically attached to the own body).

In these pages, through the description of the current literature (including our studies), we have tried to communicate to the reader the view that the representation of what pertains to the own body shapes the activity of motor and sensory systems. Here, we originally focused on the top-down modulation that the sense of body ownership exerts on sensorimotor systems. Conversely, previous literature has largely investigated the relationship in the inverse direction (Blanke et al., 2015; Ferri et al., 2012; Fossataro, Bruno, Giurgola, et al., 2018; Frassinetti et al., 2011; Tsakiris et al., 2007) (see Fig. 33), showing that sensory and motor afferent inputs are able to modify the sense of body ownership. Under normal circumstances, afferent and efferent inputs are coherent and consistent with the consolidated body-related model. However, experimental manipulations inducing changes in body ownership upon sensorimotor incongruencies show that the representation of the own body is constantly updated based on bottom up information. For instance, in the motor version of the RHI (Kalckert & Ehrsson, 2012), a conflict between visual (i.e., a fake hand is moving) and motor (i.e., I am moving my hand) inputs results in the incorporation of the fake hand and its movement. Similarly, as extendedly discussed, the visuo-tactile conflict elicited in the classical RHI (Botvinick & Cohen, 1998) ends up in the embodiment of the rubber hand. This literature pinpoints that, also in healthy and mature systems, the own body representation is highly plastic and dependent upon the sensorimotor inputs. Coherently, neuropsychology has largely shown that motor and sensory deficits are often associated with body ownership disturbances and, crucially, that proprioceptive deficit is necessary for developing an alteration of the own body representation (Garbarini et al., 2020; Romano et al., 2015; Romano & Maravita, 2019). However, the observation of patients with proprioceptive deficits who do not show body ownership disturbance has demonstrated that proprioceptive deafferentation might represent a necessary but not sufficient condition for pathological body ownership. This knowledge allows us to draw the conclusion that, once the own body representation is formed, we might still be able to discriminate the own body from the others’ even when deprived of any afferent sensorimotor input. An interesting challenge for our future studies will be to address the influence of sensory and motor domains on the construction of a bodily-self representation in the human ontogeny. Although, once matured, the own body representation seems to be something else from movement and sensory perception, however it has been proposed that it may emerge ontogenically thanks to the convergence of multisensory inputs within the motor developmental context (Errante et al., 2022; Klerk et al., 2021). In our previous study we showed that the most disconnected tracts in pathological embodiment are those which connect brain regions processing visual (temporal areas), tactile (somatosensory primary and associative areas) and proprioceptive (ventral premotor areas) inputs that are normally integrated to give rise to a normal sense of body ownership (Errante et al., 2022). By translating the heuristics derived from this evidence to a developmental perspective, we strongly believe that the representation of the own body emerges as a result of the learned association among different multisensory signals, i.e. visual, tactile and proprioceptive inputs (see Fig. 33). Coherently, an influential view in developmental studies has recently proposed that, through daily motor experience, foetuses and infants may align multisensory afferences (i.e., tactile, auditory and visual inputs) with proprioception, leading to the gradual emergence of own body representations (Klerk et al., 2021). In our view, foetuses, by performing limb movements and touching their faces or the uterine wall, learn to associate proprioceptive and tactile feedback. From birth, besides proprioceptive and tactile feedback, also visual feedback arising from limb movements are associated when infants observe themselves touching their body or external objects. Through the repeated observation that the own body is the only one on which sensory and motor inputs converge, a more abstract representation may be formed, leading to a mature bodily-self representation (see Fig. 33). In our future studies, we are going to verify this hypothesis by studying both prenatal and postnatal samples in a series of longitudinal experiments. To clarify at the causative level whether movement is the developmental context allowing the emergence of the own body representation, we aim to compare bodily-self representations in patients that suffered early motor deprivation (as a model of congenital motor deprivation) and patients that suffered from motor deficits later in life (as a model of acquired motor deprivation). We predict that, if early experience of multisensory contingence within the motor context is the main driver for the bodily-self development, early deprivation should prevent the construction of such a representation. Conversely, capitalizing on previous neuropsychological evidence, we expect an acquired motor deprivation to be insufficient for a body ownership disturbance to emerge.

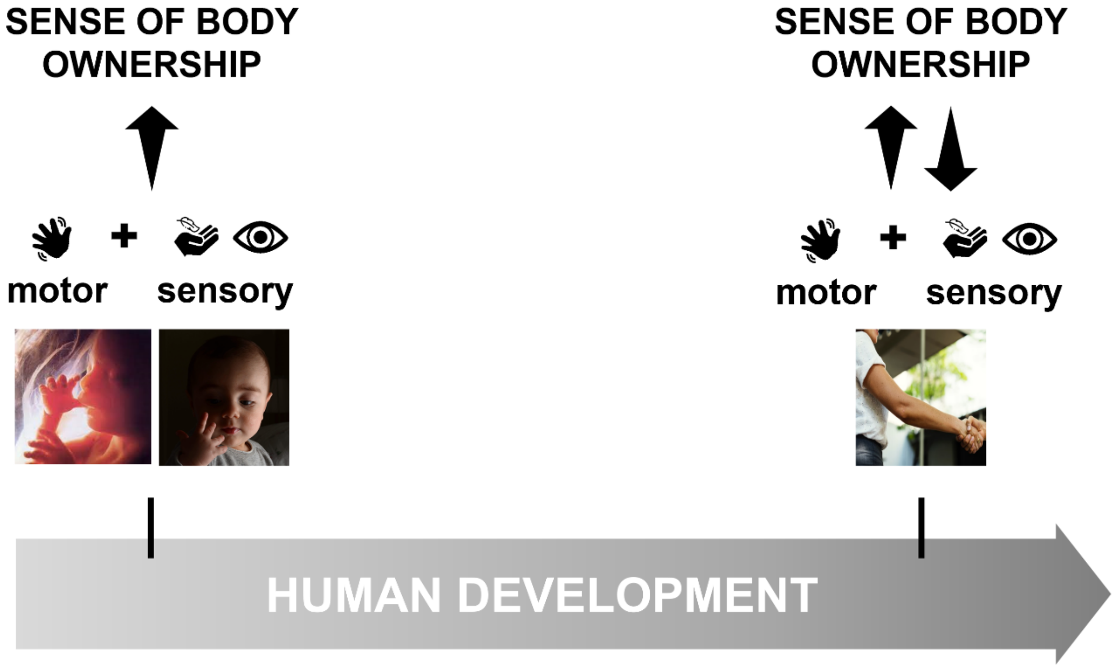

Fig. 33 Comprehensive model of the relationship between the sense of body ownership and sensory and motor domains through ontogenetic development. Early in life, foetuses and infants learn the association among different motor and sensory signals that allows the emergence of a primitive coding of what pertains to the own body (represented by the upward arrow on the left of the figure). By repeatedly observing the convergence of sensory and motor inputs, a more abstract knowledge of the bodily-self gradually emerges until a mature sense of body ownership is formed. Moreover, under normal circumstances, in the adult life, sensory and motor signals continue to nourish the body ownership representation, constantly confirming and consolidating the body-related models (note the presence of the upward arrow also on the right side of the figure). The studies presented in this dissertation show that, once the representation of the bodily-self is formed, it exerts a top-down influence of sensory perception and motor control (represented by the downward arrow on the right of the figure). Indeed, when the normal sense of body ownership is challenged either by brain damage or by bodily illusions, we move with and

perceive from the hand which is believed to be our own, even when it does not coincide with the limb that is physically attached to the own body.

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