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When Your Arm Becomes Mine: Pathological Embodiment Of Alien Limbs Using Tools Modulates Own Body Representation

Francesca Garbarini[1;2*], Carlotta Fossataro[1], Anna Berti[1;3], Patrizia Gindri[1;2], Daniele Romano[4;5], Lorenzo Pia[1;3], Francesco della Gatta[6], Angelo Maravita[4;5], Marco Neppi-Modona[1;3]

1. SAMBA (SpAtial, Motor & Bodily Awareness) Research Group, Department of Psychology, University of Torino, 10123 Torino, Italy

2. San Camillo Hospital of Torino, 10152 Torino, Italy

3. Neuroscience Institute of Torino (NIT), University of Torino, 10126 Torino, Italy

4. Department of Psychology, University of Milano–Bicocca, 20126 Milano, Italy

5. NeuroMi - Milan center for Neuroscience, University of Milano-Bicocca, 20126 Milano, Italy

6. Department of Philosophy, University of Milan, 20122 Milano, Italy

*Francesca Garbarini (Corresponding author)

Via Po 14, 10123 Turin (IT)

phone:+39 011 6703922; fax:+39 011 8159039

fra.garbarini@gmail.com; francesca.garbarini@unito.it

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Abstract

Previous evidence has shown that active tool-use can reshape one's own body schema, extending peripersonal space and modulating the representation of related body parts. Here we investigate the effect of tool-use training on length representation of the contralesional forearm in brain-damaged hemiplegic patients who manifested a pathological embodiment of other people body parts. Four patients and 20 aged-matched healthy-controls were asked to estimate the mid-point of their contralesional forearm before and after 15 min. of tool-use training (i.e. retrieving targets with a garbage plier). In the case of patients, training was always performed by the examiner's (alien) arm acting in two different positions, aligned (where the pathological embodiment occurs; E+ condition) or misaligned (where the pathological embodiment does not occur; E- condition) relative to the patients' shoulder. Healthy controls performed tool-use training either with their own arm (action condition) or observing the examiner's arm performing the task (observation condition), handling (observation with-tool condition) or not (observation without-tool condition) a similar tool. Crucially, in the E+ condition, when patients were convinced to perform the tool-use training with their own paralyzed arm, a significant overestimation effect was found (as in the Action condition with normal subjects): patients mislocated their forearm midpoint more proximally to the hand in the post- than in the pre-training phase. Conversely, in the E- condition, they did not show any overestimation effect, similarly to healthy subjects in the observation condition (neither in the with-tool nor in the without-tool condition significant overestimation effects were found). These findings show the existence of a tight link between spatial, motor and bodily representations and provide strong evidence that a pathological sense of body ownership can extend to intentional motor processes and modulate the sensory map of action-related body parts.

Keywords: Brain-damaged patients; Embodiment; Peripersonal space re-mapping ; Tool-use training; Body metric representation; Action observation.

1. Introduction

When we interact with the world around us, spatial, motor and bodily representations contribute, in different ways, to the conscious experience of the self as an acting body. We can relate this normal bodily experience to the classical concept of "body schema", firstly described by Head and Holmes (1911) as an unconscious, bottom-up, dynamic representation relying on proprioceptive information from the muscles, joints and skin. Considering the motor nature of body schema, a fundamental issue to be clarified is the nature of the relationship between body schema and motor and spatial cognition. Head and Holmes suggested that the nature of body schema is not only sensory-motor but also "action-oriented", in the sense that the possibility of action execution, intrinsic to the body function, can modulate how we represent the spatial extension of our body with respect to the external world (Gallese & Sinigaglia, 2010). Action execution, in turn, takes place in an 'action space' which can be coded as 'near' or 'far' relative to the acting body.

Near (peripersonal) and far (extrapersonal) space are behaviorally defined as the space within and beyond hand reach, respectively (Berti et al., 2001). This definition is based upon both neurophysiological evidence in the monkey and behavioural, PET and TMS evidence in humans showing that near and far space representations in the brain are anatomo-functionally dissociated. In the monkey, near space seems to be represented in frontal area 6 and in the rostral part of the inferior parietal lobe, area 7b (Leinonen, Hyvarinen, Nymani, & Linnankoski, 1979) and area VIP (Colby, Duhamel, & Goldberg, 1993; Duhamel, Bremmer, BenHamed & Graf, 1997), whereas far space is apparently coded in area 8 and area LIP (Colby, Duhamel, & Goldberg, 1996). Behavioural (Berti and Frassinetti, 1996; Maravita, Spence, & Driver, 2003; Farné, Serino, & Ladavas, 2007), PET (Weiss et al., 2000) and TMS (Lane et al., 2013) studies in humans have confirmed this dissociation. Furthermore, recent findings indicate that near and far space representations are not to be considered as static concepts, but as dynamic entities: for example, active tool-use can reshape one's own body schema, remapping near space to include the tool used to reach for objects located in far space (Maravita & Iriki, 2004, for a review). In the monkey, it has been shown that the area of visual receptive fields (vRFs) of bimodal visuo-tactile parietal neurons (known to map the subject's peripersonal space) can be modified by actions performed with tools (Iriki et al., 1996; Ishibashi et al., 2000). Indeed, the vRFs anchored to the paw were shown to encompass the entire length of the tool used to reach food located in far space, as if the tool held by the animal's hand were incorporated into the body schema. A number of studies in humans – both in brain-damaged and in healthy participants - have shown similar changes following practice to reach far visual stimuli with a tool. It has been shown that reaching with a tool a far ipsilesional target may increase the saliency of that stimulus so as to increase extinction of a contralesional tactile stimulus in patients affected by crossmodal extinction (di Pellegrino, Ladavas, & Farne 1997; see also Farnè & Ladavas, 2000; Farnè, Iriki, & Ladavas, 2005; Maravita, Husain, Clarke, & Driver, 2001). Several line-bisection studies on patients with selective neglect for near or for far space indicated that tool use can reduce or increase neglect according to the sector of space - within or outside reaching distance - where the lines are positioned (e.g., Ackroyd et al., 2002; Berti & Frassinetti, 2000; Neppi-Mòdona et al., 2007; Pegna et al., 2001). Interestingly, such a dynamical spatial remapping was modulated not only by visual and somatosensory feedbacks, but also by the modality of execution. For example, if the context required a pointing action (usually executed in far space), a far space representation was activated; if the context required a reaching action (usually executed in near space), near space was activated irrespective of the absolute spatial position of the object. Note that in this case the extension of body schema was modulated by the intentional action executed. In healthy subjects, it has been shown that the progressive increase in line bisection errors with increasing stimulus distance was abolished if participants used, instead of a laser pointer, a long stick to reach objects in far space (Longo & Lourenco, 2006). It has been also documented that tool-use may increase the impact of a visual distractor on tactile discrimination (Holmes, Calvert, & Spence 2004; Maravita, Spence, Kennett, & Driver, 2002). More importantly for the present study, a number of studies suggested that the modulatory effect of tool-use in space coding may be accompanied by a parallel change in the representations of body metrics (e.g., Bonifazi et al., 2007; Farné et al., 2007; Maravita & Driver, 2004). This hypothesis has been confirmed in a recent study (Sposito et al., 2012) showing that, in healthy subjects, active tool-use modulates the representation of related body parts; i.e. after tool-use training, participants showed an increased representation of the length of the arm handling the tool. Taken together, these findings indicate the existence of a tight relationship between body schema, action execution and space representation and that body schema is better conceptualized as the neurocognitive result of implicit sensory monitoring for action in a dynamic space. Although viewed as an unconscious representation, body schema is tightly linked to the representation of both intentional processes and spatial coding, contributing in fundamental ways to the emergence of the conscious experience of the self as an acting body in the space.

A normal interaction with the world implies the implicit notion that the body executing actions in the space is mine (not yours, not others'), i.e. it implies a normal sense of body ownership. But what happens when the sense of body ownership is dramatically altered as, for instance, after a brain damage? In brain-damaged patients with motor and somatosensory impairments, body awareness can be pathologically altered. In some cases, patients may feel a sense of strangeness towards their contralesional limbs felt as separated from their own body. The more frequent manifestation of this disorder is characterized by a sense of disownership, which is the delusional belief that the contralesional limbs do not belong to one's own body but to another person (a disturbance called somatoparaphrenia: Vallar & Ronchi, 2009; Gandola et al., 2011; Romano et al., 2014). The possibility of the existence of an opposite behavior, i.e. patients who misidentify other people's limbs as their own, has been rarely considered. However, in recent studies (Garbarini et al., 2013a; Garbarini & Pia, 2013; Pia et al., 2013a; Garbarini et al., 2014), this behavior has been observed in a sample of hemiplegic and/or hemianesthesic patients, who, while not explicitly denying that their contralesional (left) limbs belonged to themselves (as in the somatoparaphrenic delusion of disownership), claimed that the examiner's left hand was their own whenever it was positioned, in egocentric coordinates, next to their left hand. This delusion of ownership, which we called ‘embodiment’, although resembling the “rubber-hand-illusion” (Botvinick & Cohen 1998), was spontaneous and not induced by any experimental procedure. Patients treated and cared for the experimenter’s left arm as if it was their own, showing a consistent embodiment of the alien hand in their own body schema (because of this behavior, we named them ‘E+’ patients). Interestingly, this phenomenon occurs only when the alien hand is located in a position coherent with the patients’ “body image” (another classical notion introduced by Head & Holmes, 1911). The body image is considered to be a conscious, top down, cognitive representation mostly used to make perceptual judgments. It is important to consider that in E+ patients the pathological embodiment occurs only when the alien arm is in egocentric coordinates and it is aligned with the patients’ contralesional shoulder, exactly where it is expected to be according to the body image. If the position of the alien arm is misaligned with respect to the patient’s shoulder, the pathological embodiment does not occur and patients correctly discriminate their own arm/hand from the alien arm/hand (see Methods section 2.2.2 for details of how the embodiment is evaluated). Previous studies stressed the crucial role of the alignment of the alien arm with the shoulder in determining embodiment phenomena during the rubber hand illusion. Pavani and colleagues (2000) have shown that the illusion effect disappears when the fake hand is misaligned with respect to the subject's shoulder (see also Costantini and Haggard 2007, where stimulation and posture of both the real and the fake hand were manipulated, and Lloyd 2007, where the effect of proximity between the fake and the real hand was investigated). Accordingly, Farnè and co-workers (2000) described, in right-brain damaged patients, a left tactile extinction following visual stimulation of a right rubber hand. Interestingly, this cross-modal extinction was only evident when the rubber hand was aligned with the patients’ shoulder; on the contrary, when the rubber hand was misaligned with respect to the patients’ shoulder, cross-modal extinction was strongly reduced.

Critically for the present study, the pathological embodiment occurs not only with a static alien hand, but also with a moving hand: when the examiner moved his/her left hand, patients, to their surprise, claimed that they were moving their own (paralyzed) hand. Previous studies demonstrated that this phenomenon is not a mere verbal confabulation, but reflects a powerful cognitive mechanism capable of altering the patients' motor and somatosensory functions. For example, in the motor domain, these patients showed significant interference effects of the alien arm movements on the actual movements of their own intact arm (Garbarini et al., 2013a). In the somatosensory domain, when painful stimuli were delivered to the alien embodied hand, patients referred to feel pain on it (Pia et al., 2013a) and showed coherent physiological reactions, as if the own hand was stimulated (Garbarini et al., 2014).

In the present study we asked whether an altered sense of body ownership, as that shown in the delusional embodiment of alien body parts described above, can modulate both intentional motor processes and the spatial extension of the own body representation. As already mentioned, previous evidence in normal subjects has demonstrated that active tool-use modulates the representation of related body parts. It has been shown that participants estimate the mid-point of their forearm to be more distally located after a 15-min training with a 60 cm long tool, as compared to a pre training condition (Sposito et al., 2012). Here, we investigated the effects of the observation of an alien arm performing a tool-use training on the length representation of the own forearm, in both healthy subjects (Experiment 1) and in brain-damaged hemiplegic patients with a pathological embodiment of the alien arm using the tool (Experiment 2). Healthy subjects were tested in two different conditions, where they were asked a) to actually perform the tool-use training with their own arm (Action condition) or b) to observe an alien arm (the examiner's one) performing the tool-use training, while holding (Observation with-tool condition) or not (Observation without-tool condition) a similar tool (see details in Methods section 2.1.2). According to Sposito et al. (2012), we expected to find an overestimation of the forearm length only after active tool-use training (Action condition). We were also interested in verifying if this overestimation effect could be induced by simply observing an alien arm performing the tool-use training. According to Costantini et al. (2011), a difference between the observation with-tool and without-tool conditions could be expected. Indeed, these authors found that observing tool actions may extend the representation of reaching space only when observers shared the same action potentialities with the agent, i.e. while holding a tool compatible with the goal and the spatial range of the observed action.

As far as patients are concerned, in our experiment they were asked to try to perform the tool-use training with their own (paralyzed) limb, while the alien arm performed the tool-use training acting either in the E+ position, where the pathological embodiment systematically occurs, or in the E- position, where the embodiment does not occur (see details in section 2.2.2.). The crucial aspect of this experiment is that, although the task implied the observation of an alien arm performing the training (as in the Observation conditions of Experiment 1 with normal subjects), it was proposed as an active task, where hemiplegic patients were asked to try to perform the required movements with their plegic arm (see details below, section 2.2.4). On the basis of data from previous studies, in the E+ condition, we expected patients to truly believe to be actually performing the task with their own arm and, consequently, to show an overestimation of their forearm length in the post-training phase with respect to the pre-training phase (similarly to healthy subjects actually performing the task in the active condition). Conversely, in the E- condition, we expected patients to be aware of not performing the task with their own arm and, hence, not to show any overestimation of their forearm length, similarly to healthy subjects performing the task in the observation condition. If these predictions were confirmed, this would strongly support the view that the sense of body ownership not only extends to intentional motor processes but also modulates the sensory map of action-related body parts.

2. Materials & Methods

2.1. Experiment 1

2.1.1. Participants

Twenty right-handed healthy volunteers (8 females and 12 males), 57-90 years of age (mean 70,5 ± 10,6), matched for age and educational level with the sample of brain-damaged patients involved in the second experiment (see below, section 2.2.1), were recruited for the experiment. None of the subjects had a history of psychiatric or neurological disorders. All participants gave their written informed consent before taking part to the experimental procedure, which was approved by the ethical committee of the University of Turin, in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194). Participants were all naive to the experimental procedure and to the aims of the study.

2.1.2. Experimental design

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

2.1.3. Experimental procedure

The experiment comprised three phases. Firstly, participants were blindfolded and asked to perform a forearm bisection task in which they had to estimate, by means of 15 pointing movements, the mid-point of their left forearm (pre-training phase). Secondly, they were asked to perform 15 minutes of tool-use training (in free viewing). Finally, at the end of training, they were blindfolded and asked to perform again the forearm-bisection task (post-training phase). All participants performed the forearm bisection task with the right arm and the training task with the left arm (according to the literature, the effects of training are equally present on the dominant and on the non-dominant arm; Sposito et al., 2012). When we designed the Experiment 1, we chose to train the left arm because we were interested in matching the healthy subjects' performance with that of E+ patients (Experiment 2), more frequently showing a pathological embodiment for the left side of the body. Given the fact that, in the Experiment 2, we recruited also one left brain-damaged patient showing a right limb embodiment, following the suggestion of an anonymous reviewer, we additionally tested 10 right-handed age-matched healthy subjects (5 females and 5 males; 54-85 years of age (mean 68,5 ± 9,3), performing the active tool-use training with the right hand.

The forearm bisection task and the tool-use training are described in detail as follows.

Forearm bisection task: Blindfolded participants were instructed to indicate, by using their right/left index finger, the midpoint of their left/right distal upper limb segment comprising the forearm and the hand, considering the elbow and the tip of the middle finger as the two extremities. During the task, the forearm was kept in a radial posture and placed inside a plexiglas parallelepiped (70x10x11 cm), in order to prevent any possible tactile feedback from the bisections. On the top of the screen above the arm was glued a paper rule with the 0-cm scale index in correspondence of the elbow, in order to easily measure the position of the subjective midpoint (p). Then, in order to obtain a percentage score relative to each participant's subjective arm length, we used the following formula: [(p/arm length)*100]. The task was not a time trial and on-line corrections were not allowed. Each participant performed a total of 30 bisection pointings, 15 before (Pre-training) and 15 after tool-use training (Post-training) (Sposito et al., 2012). See details in Fig. 1A.

Tool use training: All participants performed the task sitting at a table. In the Action condition, they were instructed to retrieve a number of targets by means of a garbage plier (70-cm long) and put them, according to the examiner's instructions, in one of two boxes located along the right or the left side of the table. It is important to note that only distal movements were required during the training phase for triggering the plier lever with the left hand and for orienting the wrist to the left or to the right in order to grasp targets and to put them in the requested box. Targets were different from each other by color (i.e. red, yellow, blue, green), shape (i.e. circle, cube, parallelepiped) and dimension (i.e. big or small).

In the Observation condition, participants were instructed to stay still and to observe the examiner's left arm (in dark gray in Fig. 1B) performing the tool-use training with the garbage plier. They were specifically asked to focus their attention on the action performed by the examiner, orienting their gaze to the left or to the right, according to the location of the box where the examiner put the objects. The alien arm was located in a proximal position with respect to the participant's trunk midline. According to the group membership, participants were handling or not a garbage plier identical to that used by the examiner (Observation With-tool and Observation Without-tool conditions, respectively). See details in Fig. 1B.

2.1.4. Data analysis

In Experiment 1, the mean forearm bisection value of healthy subjects (n=20) was used as dependent variable. These data were entered in a 2x2x2 repeated measures ANOVA with 'tool' (two levels: 'with-tool' and 'without-tool') as between subjects factor and 'condition' (two levels: 'action' and 'observation') and 'training' (two levels: 'pre' and 'post') as within subjects factors. Planned comparisons were performed in order to compute the contrasts of interest.

Given the fact that the adopted design could potentially introduce more noise in the observation conditions (where 10 subjects performed the with-tool task and the other 10 the without-tool task) than in the action condition (where all 20 subjects performed the same task), we checked for the equivalence of variance of the active condition either versus the observation-with-tool and the observation-without-tool condition by means of F-tests for the equivalence of variance. The F-tests were not significant (Active Vs Observation-with-tool: p= .63; Active Vs Observation-without-tool: p= .11), suggesting that the equivalence of variance can be assumed and the ANOVA run properly. As suggested by an anonymous reviewer, we also run an additional ANOVA to directly test the contrast Observation-with-tool against the Observation-without-tool, ruling out the possible confound of active tool use.

Finally, to compare the left-hand training versus the right-hand training, we performed a 2 x 2 ANOVA with 'side' (two levels: 'left' and 'right') as between-subject factor and 'training' (two levels: 'pre' and 'post') as within subjects factor. The mean forearm bisection value of healthy subjects performing the left-hand training (n=20) and the right-hand training (n=10) was used as dependent variable. The equivalence of variance of the left-hand training (n=20) versus the right-hand training (n=10) was checked by means of F-tests. The F-tests were not significant (p= .43), suggesting that the equivalence of variance can be assumed and the ANOVA run properly.

2.2. Experiment 2

2.2.1. Participants

Four brain-damaged patients of cerebrovascular origin were recruited at the "San Camillo" Hospital (Turin, Italy). All participants gave their written informed consent before taking part to the experimental procedure, which was approved by the ethical committee of the ASL TO 1 of Turin and in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194). Patients were all naive to the experimental procedure and to the purpose of the study.

They were all assessed using the following tests: general cognitive tests (Montreal Cognitive Assessment – MOCA or Mini Mental State Evaluation - MMSE); visual field exam; assessment of hemiplegia, assessment of anosognosia for hemiplegia, assessment of hemianesthesia; tests for extrapersonal neglect (Behavioral Inattention Test - BIT – conventional and behavioral subtests; DILLER) and for personal neglect (FLUFF). Patients were also evaluated for somatoparaphrenia (Fotopoulou et al., 2011). Exclusion criteria were: 1) previous neurological or psychiatric history; 2) severe general cognitive impairment (patients under the MMSE cut off or the MOCA cut off were excluded); 3) visual field deficit (patients with visual field scores higher than zero were excluded). See Table 1 for details.

Patients were admitted to the study if they showed a) contralesional upper limb hemiplegia, as reported by the responsible neurologist and confirmed by a motor impairment examination carried out according to a clinical protocol (Spinazzola et al., 2008; 2014; Pia et al., 2014), with the score ranking from 0 to 3 (only patients with a score ≥ 2 were admitted); b) pathological embodiment of an alien arm (E+ patients) (Garbarini et al., 2013a; Pia et al, 2013a). Patients were classified as E+ according to the pathological embodiment evaluation (See details below, 2.2.2) described in Garbarini et al., 2013a and Pia et al, 2013a. According to this evaluation, we recruited two right-brain-damaged patients (RBD) showing left-limb-embodiment and one left-brain-damaged patient (LBD) showing right-limb-embodiment.

Patients' lesion locations were identified through MRI or CT scans. Lesions were mapped onto the MNI stereotactic space with standard MRI volume (voxels of 1 mm^3) through a computerized technique. Image manipulations were obtained with the software MRIcron (Rorden and Brett, 2000). Firstly, the MNI template was rotated on coronal, sagittal and horizontal planes according to the patient's scan angle. Secondly, a skilled rater (LP), manually mapped the lesion onto each correspondent template slice, whereas a second skilled rater (CF) double-checked for the accuracy of the tracings for each patient (in case of disagreement, an intersection lesion map was used – this occurred only once). Thirdly, the maps were back rotated into the standard space. Grey matter involvement was obtained by superimposing the Anatomical Labelling map template AAL (Tzourio-Mazoyer et al., 2002) and the JHU-white matter template (Hua et al., 2008) which categorize the distributions of digital images onto stereotactic space. Patients' brain lesions locations are consistent with those described in previous studies (Garbarini et al., 2013a; Pia et al, 2013a). The involved brain structures are shown in Fig. 2.

2.2.2. Embodiment evaluation

In order to include in the study only E+ patients, we tested them with an ad hoc protocol devised to diagnose the presence/absence of embodiment (Garbarini et al., 2013a; Pia et al, 2013a). Patients sat on a chair with both hands lying on the table. According to the patient's embodiment side (left or right, depending on the damaged hemisphere, right or left, respectively), an alien left/right hand (the examiner's one) was positioned on the table next on the patient's hand in four different positions (see Fig. 3 A-D). Note that the distance between the own and the alien hand was always the same (about 10 cm) in all conditions. The difference between conditions were: 1) the frame of reference of the alien hand position (egocentric in A, B and D and allocentric in C); 2) the alien hand-shoulder configuration (aligned with the patient's shoulder in A, C and D; misaligned in B); the alien hand body-side location (ipsilesional intact side in D; contralesional affected side in A, B and C).

Prior to the beginning of the experiment, patients underwent 3 simple tests to assess their compliance with task demands and presence or absence of the embodiment phenomenon in that specific time. A white sheet of tissue was used to cover the patient's and the examiner's arms leaving the hands visible and three cubes of different colors (red, blue and green) were placed on the table. Patients were asked 1) to count how many hands and objects were on the table; 2) to reach their paralyzed hand with their intact hand and 3) to name the color of the cube positioned in front of their own hand. In order to start the experiment, a patient had to be errorless in test 1, i.e. identify the three objects and the three hands on the table. Note that in the Embodiment condition (A), E+

the patient fail test 2, i.e. reach the alien hand instead of his/her own hand and test 3, i.e. name the color of the cube in front of the alien hand instead of naming the color of the cube in front of his/her own hand. In the control conditions (B and C), as well as on the intact (ipsilesional) body side (D), the pathological embodiment should not occur and all the patients should correctly reach/identify their own hand (see details in Fig. 3). See an example of this evaluation in Video 1.

2.2.3. Experimental design

In Experiment 2, tool-use training was always performed by the examiner's arm (in dark gray in Fig. 1C), as in the Observation condition of Experiment 1. The crucial aspect of this task is that, although it implied the observation of the alien arm performing the training, hemiplegic patients were instructed to consider it an active task, i.e. they were asked to try to perform the tool-use training with their own paralyzed arm (see details below, section 2.2.4). During the experiment, the alien arm could act in two different positions: a) aligned with the patients' shoulder, in a position more proximal to the patient's trunk midline than the own arm, where the pathological embodiment occurs (E+ condition); b) externally misaligned with respect to the patients' shoulder, in a position more distal to the patient's trunk midline than the own arm, where patients correctly recognize the alien arm as belonging to the examiner (E- condition). The experimental task (i.e. the forearm bisection task and tool-use training, see details below, section 2.2.4) involved only the patient's contralesional side (see details in Fig. 1C). The E+ and the E- conditions were performed in two experimental sessions, distanced one week from each other.

2.2.4. Experimental procedure

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

2.2.5 Ownership evaluation

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

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

2.2.6 Data analysis

In Experiment 2, the mean forearm bisection value of patients (n=4) was used as dependent variable. These data were entered in a 2x2 repeated measures ANOVA with "embodiment" (two levels: "E+" and "E-") and "training" (two levels: "pre" and "post") as within subjects factors. Planned comparisons were performed in order to compute the contrasts of interest.

Given the small sample size, we also performed a single subject analysis (non-parametric Wilcoxon test, e.g. Garbarini et al., 2013b).

Finally, in order to compare the difference in performance between pre- and post-training conditions between each single patient and the control sample, we used Crawford's test (two tailed) (Crawford et al., 2010).

3. Results

3.1 Experiment 1: healthy subjects' forearm bisection task

The ANOVA did not show any significant effect for the between-subjects factor "tool" and for all the interactions with the "tool" factor, as well as for the within-subjects factors "condition" and "training". The only significant interaction was "condition*training" ($F_{1,18}$=.15.58; p<.001). In the Action condition, there was a significant increase of the mean forearm bisection values in the post-training relative to the pre-training phase (Action pre= 41.69% ± 7.15 (St.Dev); Action post= 45.78% ± 6.9; planned comparison: $F_{1,18}$=5.061; p=.038). This means that, after training, subjects relatively overestimated their forearm length (see Fig.4). Conversely, in the Observation condition, no significant difference between pre- and post-training was found (Observation pre= 42.7% ± 7.44; Observation post= 40.46% ± 9.8; planned comparison: $F_{1,18}$=3.181; p=.093). Unexpectedly, a not significant tendency in the opposite direction (i.e. a decrease of the mean bisection values in the post- respect to the pre-training phase) was apparent (see Fig. 4).

The results of the additional ANOVA directly testing the contrast Observation-with-tool vs Observation-without-tool (ruling out the possible confound of the Action condition), show that the presence of the tool in the subject's hand was not a significant factor by itself or in the interaction with the pre/post training measurements.

The results of the additional ANOVA directly testing the contrast left-hand training vs right-hand training, show that the between-subject factor 'side' is not significant by itself or in the interaction with the pre/post training measurements. The ANOVA found a significant effect of the within-factor "training" ($F_{1,28}$=10; p<.003), suggesting that in both the left- and right-training there was a significant increase of the mean forearm bisection values in the post- with respect to the pre-training condition (see Fig. 5).

3.2 Experiment 2

3.2.1 Embodiment evaluation in E+ patients

In the E+ condition, at the end of the training phase, all patients positively answered to the first question (Did you perform the task with your left/right hand?), claiming to have performed the tool-use training with their own (paralyzed) arm. The second question (How could you perform task whit your left/right hand?) produced different answers among patients: E+ 1: "I don't know how I could do this… The task was tiring but nice!"; E+ 2: "It's easy to use this plier, only a little movement is enough to trigger the lever… can I try with the other hand?"; E+ 3: "For sure I have done this task with your (the examiner) help…". E+ 4: "I know that you (the examiner) helped me, but I have done it!". An example is shown in Video 2: E+ 1 patient is filmed while performing the tool-use training in the E+ condition and clearly shows that he is convinced to perform the task with her own arm. On the contrary, in the E- condition all patients negatively answered to the first question, correctly acknowledging that they did not perform the training with their own arm.

3.2.2 E+ patients' forearm bisection task

The ANOVA did not show significant effects for the within-subjects factors "embodiment" and "training", but, more relevant for the purpose of the study, showed significant effects for the interaction "training*embodiment" ($F_{1,3}$=38.839; p<.01). In the E+ condition, there was a significant increase of the mean forearm bisection values in the post-training relative to the pre-training phase (E+ pre= 45.40% ± 11.03 (St.Dev); E+ post= 66.36 % ± 16.21; planned comparison: $F_{1,3}$= 30.15; p=.011). This means that, after training, patients relatively overestimated their forearm length (see Fig. 5). Conversely, in the E- condition, no significant difference between pre- and post-training was found (E- pre= 64.27% ± 32.29; E- post= 55.18% ± 27.06; planned comparison: $F_{1,3}$= 5.18; p= .1). See Fig. 6.

Single subject analysis revealed that, in the E+ condition, all four patients (similarly to healthy subjects in the Action condition of Experiment 1) showed a significant increase of the bisection values in the post- with respect to the pre-training phase (Wilcoxon tests: E+1: Z = 3.29; p < .001; E+2: Z = 3.4; p < .001; E+3: Z = 3.4; p < .001; E+4: Z=3.4; p < 0.001), suggesting the presence of a consistent overestimation of forearm length after tool-use when patients were convinced to perform it with their own hand hemiplegic arm. In the E- condition, two out of four patients (E+ 1; E+ 2) did not show any difference between pre- and post-training phase; surprisingly, the other two patients showed a significant decrease of the bisection values in the post- respect to the pre-training phase (Wilcoxon test: E+3: Z = 3.4; p < .001; E+4: Z = 3.4; p < .001), suggesting the presence of a relative underestimation effect following the training (similarly to the tendency showed by healthy subjects in the Observation condition of Experiment 1). It is also apparent that, in the pre-training, forearm bisection values in the E- condition exceed those found in the E+ condition. To this respect, it must be pointed out that the difference is not significant and it is caused by the performance of 2 patients out of 4 (Wilcoxon test: $E+3_{E-vsE+:}$ Z = 3.4; p = .00065; $E+4_{E-vsE+}$: Z = 3.4; p = .00065). As suggested by an anonymous reviewer, we controlled if the ANOVA results (described above) were driven by the above reported difference in baseline values. In an ANCOVA model, where the baseline values were assumed as a covariate, we verified that the crucial interaction "training*embodiment" was still significant ($F_{1,2}$ = 33.3; p = .02), even controlling for the baseline covariate (that was not significant in itself ($F_{1,2}$ = 9; p = 1). This suggest that the difference in baselines is unlikely to have influenced our findings.

The Crawford's test (Crawford et al., 2010) was used to compare the results of each patient, tested in Experiment 2, with the results of healthy subjects in Experiment 1 (see Fig. 7). First, we tested whether the effect of tool-use training (the difference post- minus pre-training bisection values) in the E+ condition was significantly different in patients vs healthy subjects. Crawford's tests (two tailed) revealed that in three out of four patients the effect was significantly greater (E+ 1: Z DCC [difference between case and controls] = -4.826; p = .0001; E+2: Z DCC= -3.172; p = .005; E+3: Z DCC= -4.420; p = .003). Hence, this means that the relative overestimation effect after tool-use is stronger in patients than in controls. Secondly, we tested whether the effect of tool-use training (the difference post- minus pre-training bisection values) in the E+ condition was significantly different from the effect of the Observation condition in healthy subjects. Crucially, although *de facto* in the E+ condition patients observed an alien arm performing the training (similarly to controls in the Observation condition), Crawford's tests (two tailed) found a significant difference between each patient in the E+ condition and controls in the Observation condition (i.e. after tool-use patients overestimated their forearm length, whereas healthy controls tended to underestimate it) (E+ 1: Z DCC = -4.892; p = .0001; E+2: Z DCC= -3.420; p = .003; E+3: Z DCC= -3.814; p = .006; E+4: Z DCC= -2.483; p = 0.03). Finally, we compared the effect of tool use training (the difference post- minus pre-training bisection values) in the E- condition, in each patient vs healthy subjects. In two out of four patients (E+ 1; E+ 2) Crawford's tests did not find any significant difference with respect to controls. Patients E+ 3 and 4, instead, showed a relative underestimation effect of their forearm length stronger than that found in healthy subjects (E+3: Z DCC= 5.384; p = .007; E+4: Z DCC= 3.862; p = .003).

We also performed Crawford tests in order to compare the pre-training bisection values of each patient with those of the control group. In the E+ condition, we found a significant difference in one out of four patients (E+ 3: Z-CC=2.8; p=.013); in the E- condition, we found a significant difference in two out of four patients (E+3: Z-CC=9.4; p<.0001 and E+4: Z-CC=3.2; p=.004). This greater variability in the bisection task in patients than in controls, suggests that an altered body metric representation, also present in the baseline (pre-training) condition, can be associated to the body ownership disorders observed in this kind of patients.

4. Discussion

In the present work we sought for evidence that the influence of tool-use training on the body spatial representation is affected by body ownership. Two experiments were carried out, one involving healthy subjects (Experiment 1), the other involving brain-damaged hemiplegic patients with pathological embodiment of an alien arm (Experiment 2). In Experiment 1, we asked whether tool-use actions with the own arm or observing an alien arm using tools can induce comparable modulation effects on the body spatial representation. In Experiment 2, the main question was whether an altered sense of ownership of body parts (embodiment of an alien arm) 1) extends to the representation of the movement of the alien arm using tools and 2) modulates the sensory map of the own arm.

In Experiment 1, healthy subjects actually performed a tool-use training (Action condition), or observed the examiner's arm performing the training (Observation condition). In the Action condition, an overestimation effect of their forearm length was found; namely significantly greater forearm bisection values in the post- than in the pre-training phase were apparent. On the contrary, in the Observation condition, no significant difference was found, either when subjects held a similar tool in their hand (with-tool condition) or when they did not (without-tool condition). No difference between left-hand and right-hand training was found. In the experiment with hemiplegic patients (Experiment 2), although the patients were explicitly required to try to perform an active task with their own plegic arm, the tool-use training was always performed by the examiner's arm (as in the Observation condition of Experiment 1), acting in two different positions, aligned (E+) or misaligned (E-) with respect to the patients' shoulder. Crucially, in the E+ condition, where the embodiment occurred (i.e. patients were convinced to perform the tool-use training with their own (paralyzed) arm), a significant overestimation effect was found (as in the Action condition with normal subjects): patients mislocated their forearm midpoint more proximally to the hand in the post- than in the pre-training phase. Conversely, in the E- condition, when the pathological embodiment did not occur, they did not show any overestimation effect.

The results of Experiment 1 replicate previous findings (Sposito et al., 2012; Cardinali et al., 2011), confirming that, in healthy subjects, active tool-use induces dynamic changes in the representation of body metrics. In line with Sposito and co-workers findings, no training-dependent difference between the non-dominant (left) and the dominant (right) hand training was found. However, at least one study, employing different training tasks, has found significant differences between the dominant and the non-dominant hand in the augmentation of body representation following tool use (Rademaker et al., 2014). However, differently from Sposito and co-workers, healthy participants showed averages below 50% in both the pre- and the post-training conditions. This may be related to fact that the Experiment 1 sample was made of elderly individuals (57-90 years of age, mean 70,5 ± 10,6), matched for age and educational level with E+ patients tested in the Experiment 2, whereas in Sposito's experiment healthy subjects were university students. We might speculate, to this respect, that elderly subjects tend to underuse their upper (and, possibly, lower) limbs, due to restricted movement capabilities and necessities, resulting in absolute underestimation of upper (and lower) limbs length (but relative overestimation following tool-use training).

On the other hand, absence of a similar effect in the Observation condition suggests that, at least in our sample, active tool-use is necessary in order to induce dynamic changes in the body-metrics representation, whereas tool-use observation alone is not sufficient. However, some effects of tool-use observation on space representation were found in previous works. In particular, Costantini and co-workers (Costantini et al., 2011) showed that observing an alien arm performing finalized actions with a tool may extend the representation of the reaching space of the observer, but only when the latter shares the same action potentialities with the agent, i.e. when holding a tool compatible with the goal and the spatial range of the observed action. In our experiment we could not replicate this result: holding or not the same tool as the experimenter, while observing his/her arm retrieving targets with the garbage plier, did not induce spatial extension of the observer's reaching space (that is, it did not significantly influence the subject's estimation of the midpoint of his/her own forearm). A number of factors can account for the discrepancies of the results between the two experiments. Firstly, the two studies might measure a different kind of representation: a space representation in Costantini's et al. experiment, and a body representation in the present report. Even though the peripersonal space representation and the body schema are tightly linked (e.g. Cardinali, Brozzoli & Farnè, 2009), they can be measured in different ways. Secondly, the dependent variables used in the two studies are different - response time (RT) of the observer in the case of Costantini's et al. experiment, forearm bisection value in our experiment – and, therefore, might be differentially sensitive to the phenomenon investigated. It may well be the case that RT is a more sensitive measure of spatial remapping than forearm bisection. Thirdly, while it is possible that during the observation of finalized actions with a tool a mirror mechanism is activated (Rizzolatti, Fogassi, & Gallese, 2001) that is robust enough to remap the spatial representation of the observer in a RT task such as that employed in the Costantini's et al. study, it is also likely that the same mirror mechanism is not strong enough to significantly modify the sensory representation of the observer's arm in the forearm bisection task devised in our study. Indeed, appropriate visuomotor and proprioceptive feedback signals may be necessary to obtain the above mentioned remapping of the observer's arm length representation. Although very tentative, a possible explanation could be that, during the observation of finalized actions performed with a tool, the inhibitory process known to prevent the imitation of the observed actions (e.g. Stamos, Savaki & Raos, 2010; Mukamel et al., 2011), can have some role in preventing the updating of the body schema and, in turn, the body spatial remapping. It could be hypothesized that it is more demanding for the nervous system, in terms of energetic expense, to activate the plastic processes underlying the remodulation of the sensory map of one part of the body, than those necessary to remap a spatial sector (e.g. far space) into another (e.g. near space).

The above mentioned inhibitory mechanism could also be somehow related to the opposite underestimation trend, shown in the Observation condition at least in some subjects. It is worth noting that the Observation condition is crucial for distinguishing between remapping effects induced by motor activation or by attentional processing. Indeed, if attentional mechanisms could fully explain the effects found following tool-use (e.g., Holmes et al., 2004), similar results should be expected in Action and Observation conditions, where the subject's spatial attention is equally involved (in both conditions the subject has to pay attention to the tip of the garbage plier, grasping targets in far space and putting them in the requested box); and this is not the case.

In Experiment 2, instead, E+ patients showed an overestimation of their own forearm length after tool-use training performed by the alien (embodied) arm. This clearly suggests that an altered sense of body ownership of someone else's arm can extend to intentional motor processes and modulate own body spatial representation. Furthermore, comparing the results of single patients with those of the sample of healthy subjects, the overestimation effect revealed by each patient during the E+ condition was greater than that found in healthy subjects during the Active condition (the difference was significant in three out of four patients at Crawford test), suggesting that when body awareness is selectively impaired, the body-metrics representation is more susceptible to be altered.

According to previous studies (e.g. Garbarini et al., 2012; Pia et al. 2013b; Garbarini et al., 2013a; Gondola et al., 2014), hemiplegic patients fully aware of their paralysis, when asked to try to perform motor acts with their paralyzed hand/arm, do not produce any effective motor programming. However, when a pathological embodiment occurs, as in the E+ condition of our experiment, the delusion of ownership affects both motor awareness and the sense of agency (patients, although not anosognosic before the task – see Table 1 - are firmly convinced to perform the tool-use training with their own plegic arm). This, in turn, might automatically trigger intentional motor processes for the own plegic arm, which generate the updating of the body schema and lead to the remapping of one's own forearm length (similarly to healthy subjects actually performing the tool use training in the Active condition). It is important to note that the delusion of ownership, as it is also evident in the rubber hand illusion (Pavani et al., 2000; Farnè et al., 2000; Costantini & Haggard, 2007), is observed only when the alien hand is located, in egocentric coordinates, in a plausible position, compatible with the observer body schema. If this condition is not fulfilled, as in the E- condition of our experiment where the alien hand is misaligned with respect to the patients' shoulder, the embodiment does not occur. In this case, patients immediately ascribe the movements to the examiner's arm and, although required to try to perform the task as in the E+ condition, *de facto* observed the examiner performing the task, and do not show any significant remapping of their forearm length, similarly to healthy subjects during Observation conditions. According to Cardinali and co-workers (2009) "the body schema does not accept any incoherence. This mean that when a conflict occurs between two inputs" - as, in our case, two left/right hands on the table -, "the brain solves it in the direction of one of them" (p. 5). We can speculate that, in this kind of patients, when the body representation is altered, the more coherent position for the arm/hand (i.e. when the arm is perfectly aligned with the shoulder and close to the body) can orient the patients' sense of body ownership.

Finally, in the observation condition, it must be acknowledged the presence of a non significant tendency towards underestimation one's own arm length in the majority of control subjects and in two out of four patients. This tendency was significantly greater in the two patients than in healthy subjects. These results were unexpected and we do not have yet a convincing explanation for it. Nevertheless they might be worth of further investigation in their own right on a larger sample of patients. The possibility exists that they are related to a specific inhibitory mechanism activated during the observation of someone else's finalized actions preventing action execution when contextual conditions (passive observation of someone else's movement or imaging one's own movement) are inadequate to trigger the anticipatory neurocognitive plastic processes (e.g. space and body metrics remapping) subserving a future action.

From an anatomical point of view, previous studies (Garbarini et al., 2013a; Pia et al, 2013a) described left-side embodiment following right-brain damage. Here, for the first time, a right-side embodiment following left-brain damage was described in patient E+1 (see Fig. 2). This suggests that, although it seems to be more frequently associated to right-brain lesions, this phenomenon is not related to a specific function of the right hemisphere. Although this datum needs further investigation on a larger sample of patients, it suggests the presence of a right hemisphere dominance for the building of the sense of body ownership rather than an absolute lateralization of this function in the right hemisphere (see also Tsakiris, Costantini, & Haggard, 2008). According to previous studies (Garbarini et al., 2013a; Pia et al, 2013a), pathological embodiment is related to damage to subcortical motor structures (basal ganglia: globus pallidus, putamen) and periventricular white matter. Lesions locations of patients tested here is compatible with this pattern (see Fig. 2), that is also consistent with the one identified for being responsible for somatoparaphrenia (Gandola et al., 2012), thus suggesting a common locus for the two complementary body awareness disorders. Following Gandola et. al. interpretation, we can hypothesize that a damage to the white matter tract linking subcortical structures with cortical sensory-motor and associative areas may prevent the integration of afferent information arising from the affected body part (bottom-up processes) with higher-order and pre-existing body representations (top-down processes) leading to a deficit in the construction of a coherent body representation (Tsakiris et al., 2006, 2007, 2008). We may speculate that when the representation of the contralesional hand is partially impaired or made fragile by the brain damage, as in E+ patients, the brain solves the incoherence of the 'mutilated' body representation by automatically incorporating an alien hand so to regain consistency and functionality.

In conclusion, these findings demonstrate that, in presence of a delusion of ownership of a body part, the alien body part can be so deeply incorporated into one's own body schema to extend to action execution and to induce measurable dynamic changes in the body-metrics representation comparable to those observed during really executed movements. This phenomenon is still far from being fully understood at the level of its neurocognitive mechanisms and a number of important questions still need to be answered. For example, the role of motor intentionality in the emergence of the sense of body ownership needs to be more deeply investigated. Does embodiment of an alien arm equally develops in absence of intention to move the own paralyzed arm, e.g. if the patient is asked to passively observe someone else's arm movement? Or, else, do patients with embodiment show similar remapping of one's own hemiplegic arm's length representation when asked only to imagine to reach for far objects with a tool?

Despite being only on the verge of a full understanding of the embodiment phenomenon, the so far collected experimental results, if further confirmed on a larger sample of patients, might have important fallbacks in the domain of neuropsychological rehabilitation. For example, it could be the case that hemiplegic patients with embodiment of an alien arm might benefit more from an observational motor training (i.e. a motor training actually performed by an alien arm) than a passive motor training, where embodiment does not occur.

Limitations of the study

We acknowledge a number of limitations of the present study: 1) the design adopted in both elderly controls (Experiment 1) and brain-damaged patients (Experiment 2) was not the ideal one. In both experiments, in order to avoid sequence effects, patients and controls were tested in two different experimental sessions (at one week distance) and we preferred not to add further experimental sessions, although this choice compromised the optimal full within-subject design, with three experimental sessions in Experiment 1 (Action; Observation with-tool; Observation without-tool) and with four experimental sessions in Experiment 2 (E+ condition with- and without-tool; E- condition with- and without-tool). 2) different instructions were –necessarily- given to control subjects in the Observation conditions (they were requested to stay still and to observe the examiner's arm performing the task), and to patients in the E+ and E- conditions (they were required to perform an "active" task, being asked to 'try' to use the garbage plier with their plegic hand), thus rendering the two experiments not fully comparable. On the one hand, in Experiment 1, the Observation conditions (with- and without-tool) were introduced in order to exclude the possibility that a visual feedback alone (vision of the alien arm using the tool) can be able to alter the body metric representation. If so, all the effects found in patients could be ascribed to the visual feedback and not to the pathological embodiment; on the other hand, in Experiment 2, in order to compare the results of the patients' E+ and E- conditions with those found in healthy controls actually performing the tool-use training, it was crucial to ask the patients to perform an active task.

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References

Ackroyd K., Riddoch M.J., Humphreys G. W., Nightingale S. & Townsend S. (2002). Widening the Sphere of Influence: Using a Tool to Extend Extrapersonal Visual Space in a Patient with Severe Neglect. *Neurocase, 8*, 1-12.

Berti A. & Frassinetti F. (2000). When far becomes near: re-mapping of space by tool use. *Journal of Cognitive Neuroscience, 12*, 415–420.

Botvinick M. & Cohen J. (1998). Rubber hands 'feel' touch that eyes see. *Nature, 391*, 756.

Bonifazi S., Farnè A., Rinaldesi L. & Ladavas E. (2007). Dynamic size-change of peri-hand space through tool-use: spatial extension or shift of the multi-sensory area. *Journal of Neuropsychology, 1*, 101–114.

Cardinali L., Brozzoli C., & Farnè A. (2009). Peripersonal space and body schema: two labels for the same concept? *Brain Topogr*, *21*, 252-60.

Cardinali L., Brozzoli C., Urquizar C., Salemme R., Roy A. C., & Farnè A. (2011). When action is not enough: Tool-use reveals tactile-dependent access to Body Schema. *Neuropsychologia, 49*, 3750–7.

Colby, C. L., Duhamel, J. R., and Goldberg, M. E. (1993). Ventral intraparietal area of the macaque: Anatomic location and visual response properties. *J. Neurophysiol*. *69*, 902–914.

Colby, C. L., Duhamel, J. R., and Goldberg, M. E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J. Neurophysiol. 76*, 2841–2852.

Costantini M. & Haggard P. (2007). The rubber hand illusion: Sensitivity and reference frame for body ownership. *Consciousness and Cognition, 16*, 229-240.

Costantini M., Committeri G. & Sinigaglia C. (2011). Ready Both to Your and to My Hands: Mapping the Action Space of Others. *PLoS ONE, 6*, e17923.

Crawford J. R., Garthwaite P. H. & Porter S. (2010). Point and interval estimates of effect sizes for the case-controls design in neuropsychology: Rationale, methods, implementations, and proposed reporting standards. *Cognitive Neuropsychology, 27*, 245-260.

di Pellegrino G., Làdavas E. & Farné A. Seeing where your hands are. (1997). *Nature, 388*, 730-730?.

Farnè A., Pavani F., Maneghello F. & Ladavas E. (2000). Left tactile extintion following visual stimulation of a rubber hand. *Brain*, *123*, 2350-60.

Farnè A., Iriki A. & Ladavas E. (2005). Shaping multisensory action-space with tools: evidence from patients with cross-modal extinction. *Neuropsychologia, 43*, 238–248.

Farnè A. & Ladavas E. (2000). Dynamic size-change of hand peripersonal space following tool use. *Neuroreport, 11*, 1645–1649.

Farnè A., Serino A. & Ladavas E. (2007). Dynamic size-change of peri-hand space following tool-use: determinants and spatial characteristics revealed through cross-modal extinction. *Cortex, 43*, 436–443.

Fotopoulou A., Jenkinson P. M., Tsakiris M., Haggard P., Rudd A., & Kopelman M. D. (2011). Mirror-view reverses somatoparaphrenia: dissociation between first- and third-person perspectives on body ownership. *Neuropsychologia, 49*, 3946-3955.

Gallese V. & Sinigaglia C., (2010). The bodily self as power for action. *Neuropsychologia, 48*, 746-55.

Gandola M., Invernizzi P., Sedda A., Ferrè E. R., Sterzi R., Sberna M., Paulesu E. & Bottini G. (2012). An anatomical account of somatoparaphrenia. *Cortex, 48*, 1165-78.

Gandola M., Bottini G., Zapparoli L., Invernizzi P., Verardi M., Sterzi R., Santilli I., Sberna M. &

Paulesu E. (2014). The physiology of motor delusions in anosognosia for hemiplegia: Implications for current models of motor awareness. *Consciousness and Cognition, 24*, 98–112.

Garbarini F., Fornia L., Fossataro C., Pia L., Gindri P. & Berti A. (2014). Embodiment of others' hands elicits arousal responses similar to one's own hands. *Current Biology (in press).*

Garbarini F., Rabuffetti M., Piedimonte A., Pia L., Ferrarin M., Frassinetti F., Gindri P., Cantagallo A., Driver J. & Berti A., (2012). 'Moving' a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia. *Brain, 135*, 1486–1497.

Garbarini F. & Pia L. (2013). Bimanual coupling paradigm as an effective tool to investigate productive behaviors in motor and body awareness impairments *Frontiers in Human Neuroscience,* 7, 1-5.

Garbarini F., Pia L., Piedimonte A., Rabuffetti M., Gindri P., Berti A. (2013a) Embodiment of an alien hand interferes with intact-hand movements. *Current Biology, 23*, 2-r57-R58.

Garbarini F., Piedimonte A., Dotta E., Pia L. & Berti A. (2013b). Dissociations and similarities in motor intention and motor awareness: the case of anosognosia for hemiplegia and motor neglect. *Journal of Neurology, Neurosurgery and Psychiatry, 84*, 416-419.

Head H. & Holmes G. (1911). Sensory disturbances from cerebral lesions. *Brain, 34*,102-245.

Holmes, N. P., Spence, C., Hansen, P. C., Mackay, C. E., & Calvert, G. A. (2008). The multisensory attentional consequences of tool use: a functional magnetic resonance imaging study. *PLoS One, 3*, e3502.

Hua K., Zhang, J., Wakana S., Jiang H., Li X., Reich D. S., Calabresi P. A., Pekar J. J., van Zijl P. C. & Mori S. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage, 39*, 336-347.

Iriki A., Tanaka M. & Iwamura Y. (1996). Coding of modified body schema during tool use by macaque postcentral neurones. *Neuroreport, 7*, 2325–2330.

Lane A.R., Ball K, Smith D.T., Schenk T, & Ellison A. (2013) Near and far space: understanding the neural mechanisms of spatial attention. *Human Brain Mapping 34*, 356–366.

Lloyd D.M. (2007). Spatial limits on referred touch to an alien limb may reflect boundaries of visuo-tactile peripersonal space surrounding the hand. *Brain and Cognition*, *64*, 104-109.

Longo M. R. & Luorenco S. F. (2006). On the nature of near space: Effects of tool use and the transition to far space. *Neuropsychologia, 44*, 977-981.

Ishibashi H., Hihara S. & Iriki A. (2000). Acquisition and development of monkey tool-use: behavioural and kinematic analyses. Can. J. Physiol. *Pharmacol. 78*, 1–9.

Maravita A., Clarke K., Husain M. & Driver J. (2002). Active tool use with the contralesional hand can reduce cross-modal extinction of touch on that hand. *Neurocase, 8*, 411–416.

Maravita A. & Driver J. (2004). Crossmodal integration and spatial attention in relation to tool-use and mirror-use: representing and extending multimodal space near the hand. In: G. Calvert, C. Spence, & B. Stein (Eds.), *Handbook of multisensory processes* (pp. 819–835). Cambridge MA: MIT Press.

Maravita A. & Iriki A. (2004). Tools for the body (schema). *Trends in Cognitive Sciences, 8*, 79–86.

Maravita A., Spence C., Kennett S. & Driver J. (2002). Tool-use changes multi- modal spatial interactions between vision and touch in normal humans. *Cognition, 83*, B25–B34.

Maravita A., Spence C. & Driver J. (2003). Multisensory integration and the body schema: close to hand and within reach. *Current Biology, 13*, 53.

Masson M. E. J. & Loftus G. R. (2003). Using confidence intervals for graphically based data interpretation. *Canadian Journal of Experimental Psychology/Revue Canadienne de Psychologie Expérimentale*, *57*, 203–220.

Mukamel R., Ekstrom A. D., Kaplan J., Iacoboni M. & Fried I. (2010). Single-neuron responses in humans during execution and observation of actions. *Current Biology. 20*, 750-6.

Neppi-Mòdona M., Rabuffetti M., Folegatti A., Ricci R., Spinazzola L., Schiamone F., Ferrarin M. & Berti A. (2007) Bisecting lines with different tools in right brain damaged patients: the role of action programming and sensory feedback in modulating spatial remapping. *Cortex, 43,* 397-410.

Pavani F., Spencer C. & Driver J. (2000). Visual capture of touch: out of the body experience with rubber gloves, *Psychol Sci*, *11*, 353-9.

Pegna A. J., Petit L., Caldara-Schnetzer A. S., Khateb A., Annoni J. M., Sztajzel R. and Landis T. (2001). So near yet so far: neglect in far or near space depends on tool use. *Annals of Neurology, 50*, 820–822

Pia L., Garbarini F., Fossataro C., Fornia L. & Berti A. (2013a). Pain and body awareness: evidence from brain-damaged patients with delusional body ownership. *Frontiers in Human Neuroscience, 7*, 298.

Pia L., Spinazzola L., Rabuffetti M., Ferrarin M., Garbarini F., Piedimonte A., Driver J. & Berti A. (2013b) Temporal coupling due to illusory movements in bimanual actions: Evidence from anosognosia for hemiplegia. *Cortex, 49*, 1694-1703.

Pia L, Spinazzola L, Garbarini F, Bellan G, Piedimonte A, Fossataro C, Livelli A, Burin D, Berti A (2014). Anosognosia for hemianaesthesia: a voxel-based lesion-symptom mapping study. *Cortex (in press).*

Rademaker R.L., Wu D.A., Bloem I.M., Sack A.T. (2014). Intensive tool-practice and skillfulness facilitate the extension of body representations in humans. *Neuropsychologia*, *56*, 196-203.

Rizzolatti G., Fogassi L. & Gallese V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nature Reviews Neuroscience, 2*, 661-670.

Rorden C. & Brett M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology, 12*, 191–200.

Romano D., Gandola M., Bottini G. & Maravita A. (2014). Arousal responses to noxious stimuli in somatoparaphrenia and anosognosia: clues to body awareness. *Brain, 137*, 1213–1223.

Spinazzola L., Pia L., Folegatti A., Marchetti C. & Berti A. (2008). Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. *Neuropsychologia, 46*, 915–26.

Spinazzola L, Bellan G, Pia L, Berti A (2014). Unawareness of Motor and Somatosensory deficits after stroke (UMAS): Validity and Reliability of UMAS Questionnaire. *Applied Psychology Bullettin (in press).*

Sposito A., Bolognini N., Vallari G. & Maravita A. (2012). Extension of perceived arm length following tool-use: Clues to plasticity of body metrics. *Neuropsychologia, 50*, 2187–2194.

Stamos A. V., Savaki H. E. & Raos V. (2010). The Spinal Substrate of the Suppression of Action during Action Observation. *The Journal of Neuroscience 30*, 11605-11611.

Tsakiris M., Costantini M., & Haggard P. (2008). The role of the right temporo-parietal junction in maintaining a coherent sense of one's body. *Neuropsychologia, 46*, 3014-3018.

Tsakiris M., Hesse M. D., Boy C., Haggard P. & Fink G. R. (2007) Neural signatures of body ownership: A sensory network for bodily self-consciousness. *Cerebral Cortex, 17*, 2235-2244.

Tsakiris M., Prabhu G. & Haggard P. (2006). Having a body versus moving your body: How agency structures body-ownership. *Consciousness and Cognition*, *15*, 423-432.

Tzourio-Mazoyer N., Landeau B., Papathanassiou D., Crivello F., Etard O., Delcroix N., Mazoyer B. & Joliot M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*, 273–289.

Vallar G. & Ronchi R. (2009). Somatoparaphrenia: a body delusion. A review of the neuropsychological literature. *Experimental brain research, 192*, 533-551.

Weiss, P. H., Marshall, J. C., Wunderlich, G., Tellmann, L., Halligan, P. W., Freund, H. J., Zilles, K., and Fink, G. R. (2000). Neural consequences of acting in near versus far space: A physiological basis for clinical dissociations. *Brain 123*, 2531–2541.

TABLE

	E+ PATIENTS			
PATIENT	E+1	E+2	E+3	E+4
AGE	50	65	72	48
SEX	F	M	M	M
EDUCATION	5	17	8	5
ETIOLOGY	I	I	I	H
LESION SIDE	LH	RH	RH	RH
MONTHS FROM ONSET	6	3	2	2
VISUAL FIELD DEFECT	0-0	0-0	0-0	0-0
HEMIPLEGIA (HP)	3	2	3	3
ANOSOGNOSIA FOR HP	0	0	0	0
HEMIANESTHESIA (HAE)	3	1	2	3
GENERAL COGNITIVE IMPAIRMENT	-	-	-	-
EXTRAPERSONAL NEGLECT	+	-	+	+
PERSONAL NEGLECT	-	-	-	-
SOMATOPARAPHRENIA	-	-	-	-

Table 1. Patients' demographic and clinical data

Presence of embodiment (E+) of the experimenter's arm. Sex: M = Male, F = Female. Education: years of school. Etiology: H = hemorrhage; I = ischemia. Lesion Side: RH = Right Hemisphere; LH = Left Hemisphere. Months from onset: number of months between the onset of the disease and the first assessment. For visual field defect (the two values refer to the upper and lower visual quadrants, respectively), hemiplegia, anosognosia for hemiplegia and hemianesthesia scores were ranged from normal (0) to severe defects (3) (Spinazzola et al., 2008; 2014; Pia et al., 2014). General cognitive impairment (- = no deficit; + = presence of deficit;): MOCA cut off ≥ 14.5/30;

MMSE cut off ≥ 24/30. Extrapersonal neglect (- = no deficit; + = presence of deficit;): BIT, conventional subtests cut-off ≥ 129/146; BIT behavioral subtest cut-off ≥ 67/81; DILLER cut-off omissions l–r ≥ 5. Personal neglect (- = no deficit; + = presence of deficit;): FLUFF cut off omissions L ≤ 2. The presence/absence of somatoparaphrenia was evaluated according to Fotopoulou et al., 2011.

FIGURE CAPTIONS

Figure 1. Experimental task

A) *Bisection task*: schematic aerial view of the experimental setting depicting the forearm bisection procedure in Experiments 1 and 2; the subject's arm lied inside a translucid plexiglas parallelepiped to avoid tactile feedback. The numbers on top represent the paper ruler used to calculate the subjective midpoint in cm (see section 2.1.3 for details).

B) *Tool-use training, Experiment 1*: Healthy volunteers performed the training either with their own arm (Action condition) or observing the examiner's arm (the dark gray one) perform the task, handling (Observation with-tool condition) or not (Observation without-tool condition) a similar tool.

C) *Tool-use training, Experiment 2:* with patients the training was performed by the examiner's (alien) arm (in dark gray). The alien arm could act a) in a position more proximal to the patient's trunk midline (E+ condition**,** upper left and right quadrants), where embodiment occurs, or b) in a more distal position (E- condition**,** lower left and right quadrants), where embodiment does not occur and patients correctly acknowledge that the alien arm belongs to the examiner. The task was performed on the patients' contralesional side.

Figure 2. Patients' lesion reconstruction

E+1. Left-hemisphere lesions, involving: hippocampus, amygdala, middle temporal pole, parahippocampal gyrus, fusiform gyrus, heschl gyrus, temporo-parietal periventricular white matter.

E+2. Right-hemisphere lesions, involving: superior longitudinal fasciculus, anterior limb of internal capsule, external capsule, putamen, globus pallidus, fronto-parietal periventricular white matter.

E+3. Right-hemisphere lesions, involving: supramarginal gyrus, middle temporal pole, heschl gyrus, uncinate fasciculus, cingulum (hippocampus), posterior thalamus, retrolenticular part of internal capsule, putamen, sagittal stratum and temporo-parietal periventricular white matter**.**

E+4: Right-hemisphere lesions, involving: precentral gyrus, inferior frontal operculum, inferior frontal gyrus (triangular part), inferior frontal gyrus (orbital part), rolandic operculum, insula, postcentral gyrus, supramarginal gyrus, angular gyrus, heschl gyrus, suoperioir temporal gyrus, temporal pole (superior part), middle temporal gyrus. fronto-temporo-parietal periventricular white matter.

Figure 3. Embodiment evaluation

An alien left/right arm (the examiner's one) was positioned on the table in four different conditions:

A) The alien arm (in grey) is aligned with the patient's contralesional shoulder, in a position more proximal to the patient's trunk midline than the own arm (Shoulder alignment condition).

B) The alien arm (in grey) is (externally) misaligned with respect to the patient's contralesional shoulder, in a position more distal with respect to the patient's trunk midline than the own arm (Shoulder misalignment condition).

C) The alien arm (in grey) is placed in a position more proximal to the patient trunk midline (as in A) but in an allocentric position, i.e. facing the patient (Allocentric condition).

D) The alien arm (in grey) is aligned with the patient's ipsilesional shoulder, in a position more proximal to the patient's trunk midline than the own arm (Intact-side condition).

The patient was asked: 1) to count how many hands and objects were on the table; 2) to reach his/her own hemiplegic hand with his/her own non plegic ipsilesional hand and 3) to identify his/her own hand on the basis of the color of the object facing the hand. In all conditions the patient counts three objects (blue, red and green) and three hands (question 1). In A) (lower part) the patient reaches the alien hand (the grey one) (question 2) and identifies his/her own hand as the one in front of the blue cube (question 3); in B) (lower part) the patient correctly reaches his/her own hand (the pink one) (question 2) and identifies it as the one facing the red cube (question 3); in C) (lower part) the patient correctly reaches his/her own hand (question 2); in D) (lower part) the patient correctly identifies his/her own hand as the one facing the red cube (question 3). Note that in D) question 2 was not administered: given the contralesional paralysis, patients could not reach for the intact hand with the affected hand.

Figure 4. Results of Experiment 1: Action vs Observation

Graphic representation of normal subjects' (N=20) mean forearm bisection values (in %) in the pre-training (PRE) and in the post-training phase (POST) during the Action (in red) and the Observation (in blue) conditions. ***P< .0001; **P< .001; *P< .01

Figure 5. Results of Experiment 1: Dominant hand vs Non-dominant hand

Graphic representation of the mean forearm bisection values (in %) in normal subjects performing the active tool-use training with the dominant (right) hand (N=10) (in red) or with the non-dominant (left) hand (N=20) (in blue) in the pre- (PRE) and post-training (POST) conditions. The effect of training is significant (*P< .01) with no difference between training performed with the left (non dominant) or right (dominant) hand.

Figure 6. Results of Experiment 2: E+ condition vs E- condition

Graphic representation of patients' (N=4) mean forearm bisection values (in %) in the pre-training (PRE) and in the post-training phase (POST) during the left/right arm E+ condition (in red) and the left/right arm E- condition (in blue). ***P< .0001; **P< .001; *P< .01.

Figure 7. Comparison between patients (Experiment 2) and healthy subjects (Experiment 1)

A. Bar plot showing the effect of tool use training (Post-Pre) on Arm's length estimation in single patients and in control subjects (E+ and Action condition, respectively). A general overestimation effect is evident. Overestimation effects in single patients are compared with those in the control group. **B**. Bar plot showing the effect of tool use Observation (Post-Pre) on Arm's length estimation in single patients and in control subjects (E- and Observation condition, respectively). A general tendency to underestimation of arm length is apparent. Underestimation effects in single patients are compared with those in the control group. ***P< .0001; **P< .001; *P< .01

Figure 1

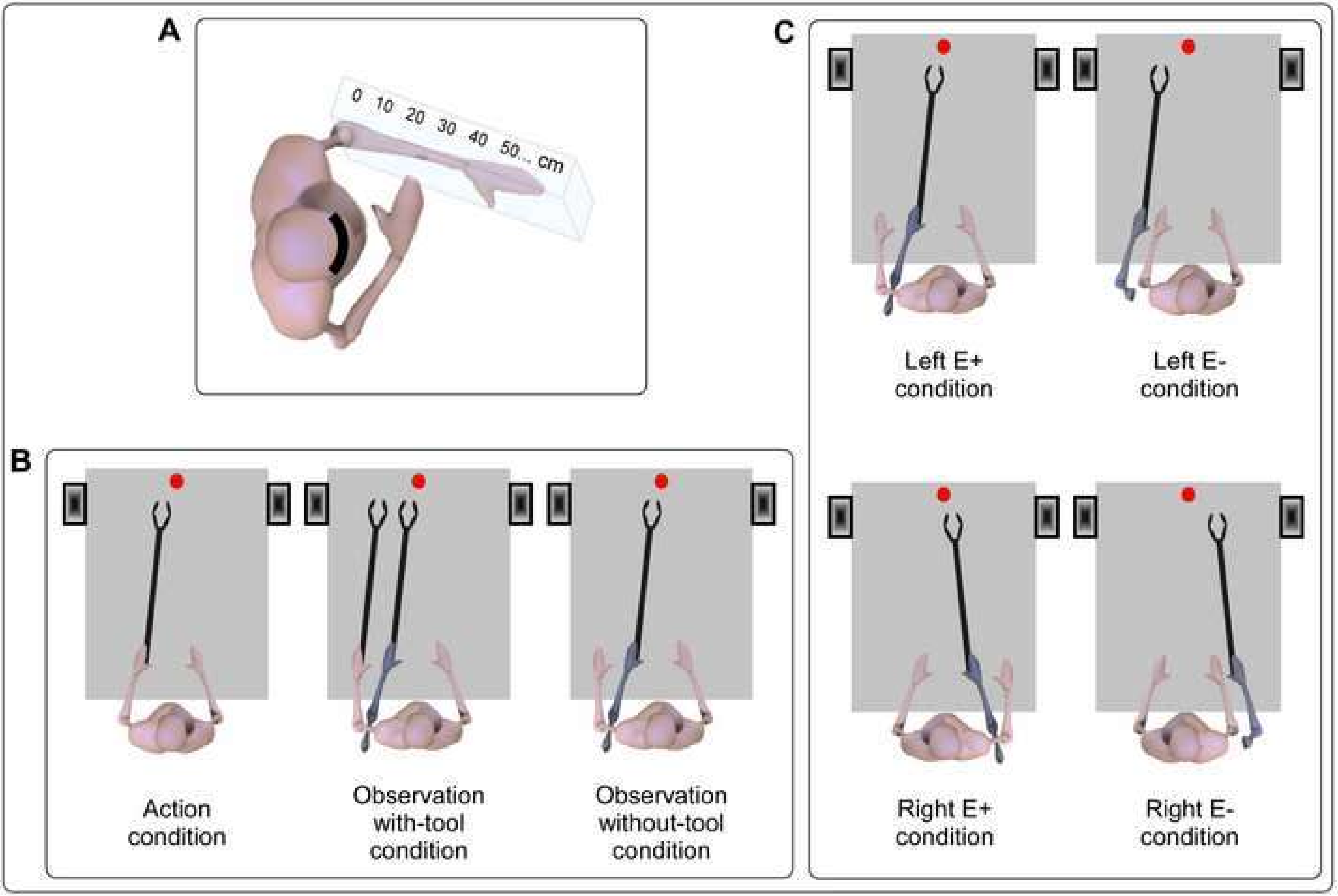
A
0 10 20 30 40 50... cm
B
Action condition
Observation with-tool condition
Observation without-tool condition
C
Left E+ condition
Left E- condition
Right E+ condition
Right E- condition

Figure 2
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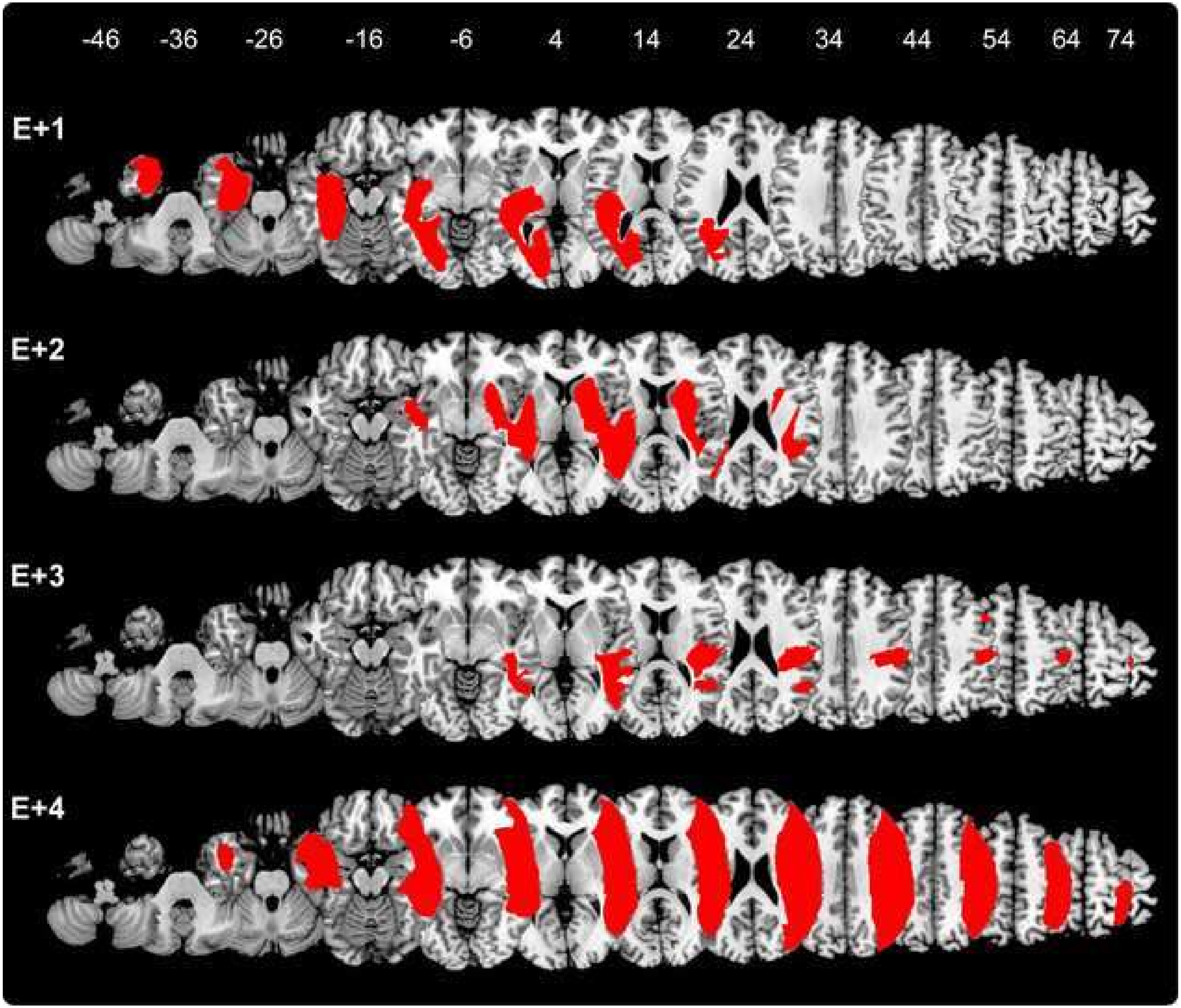

Figure 3
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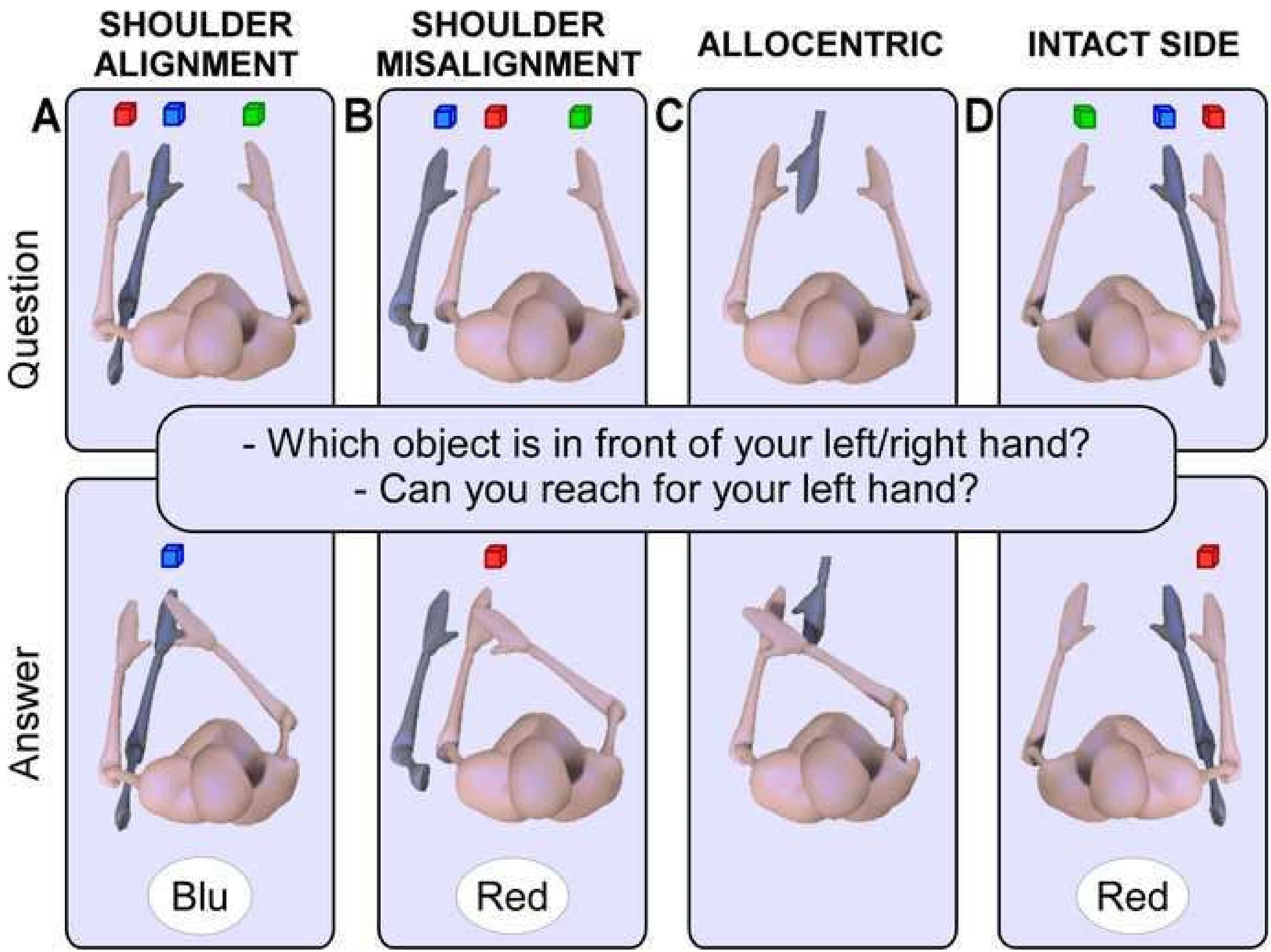

Figure 4

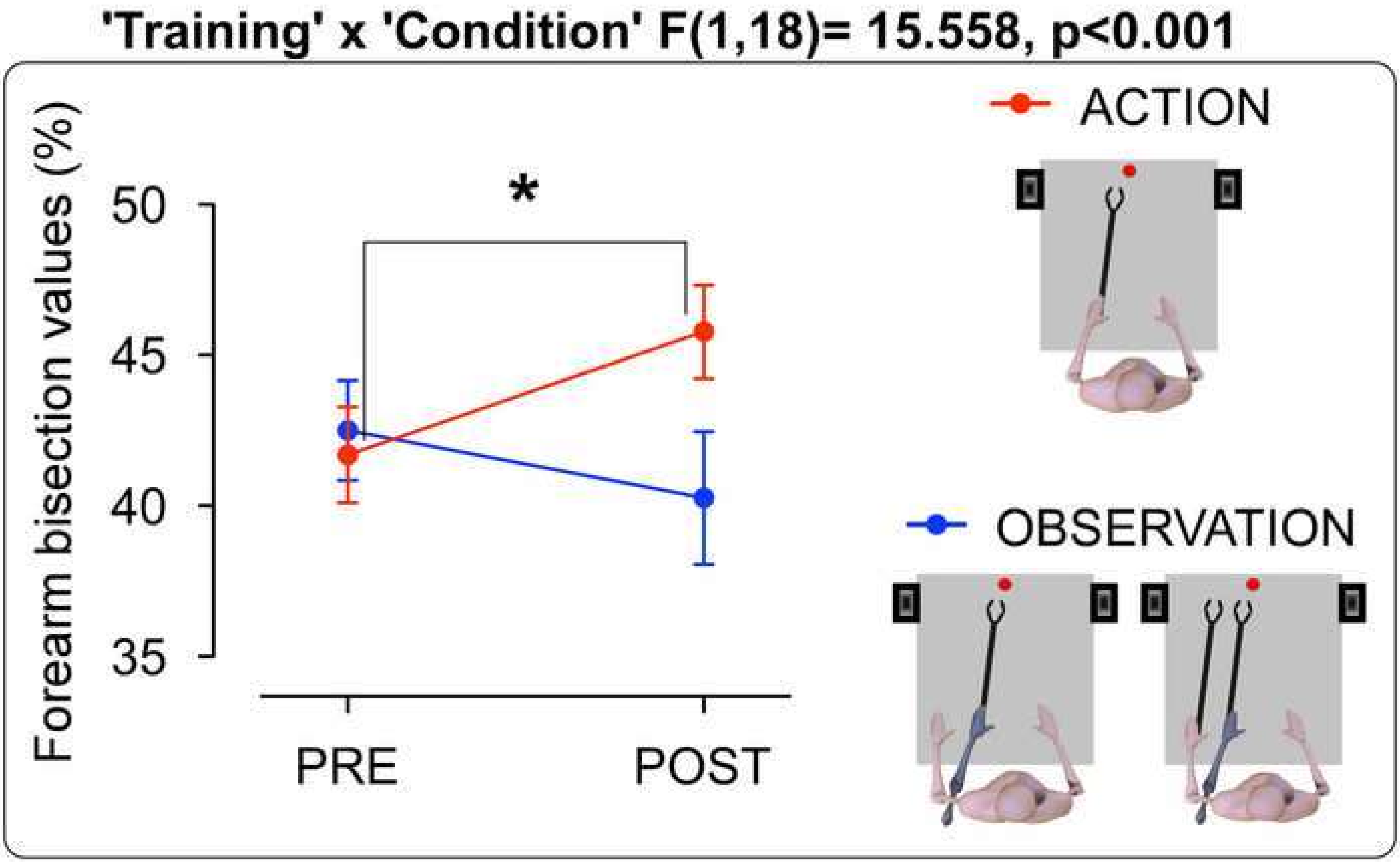
'Training' x 'Condition' F(1,18)= 15.558, p<0.001
Forearm bisection values (%)
50
45
40
35
*
PRE
POST
ACTION
OBSERVATION

Figure 5

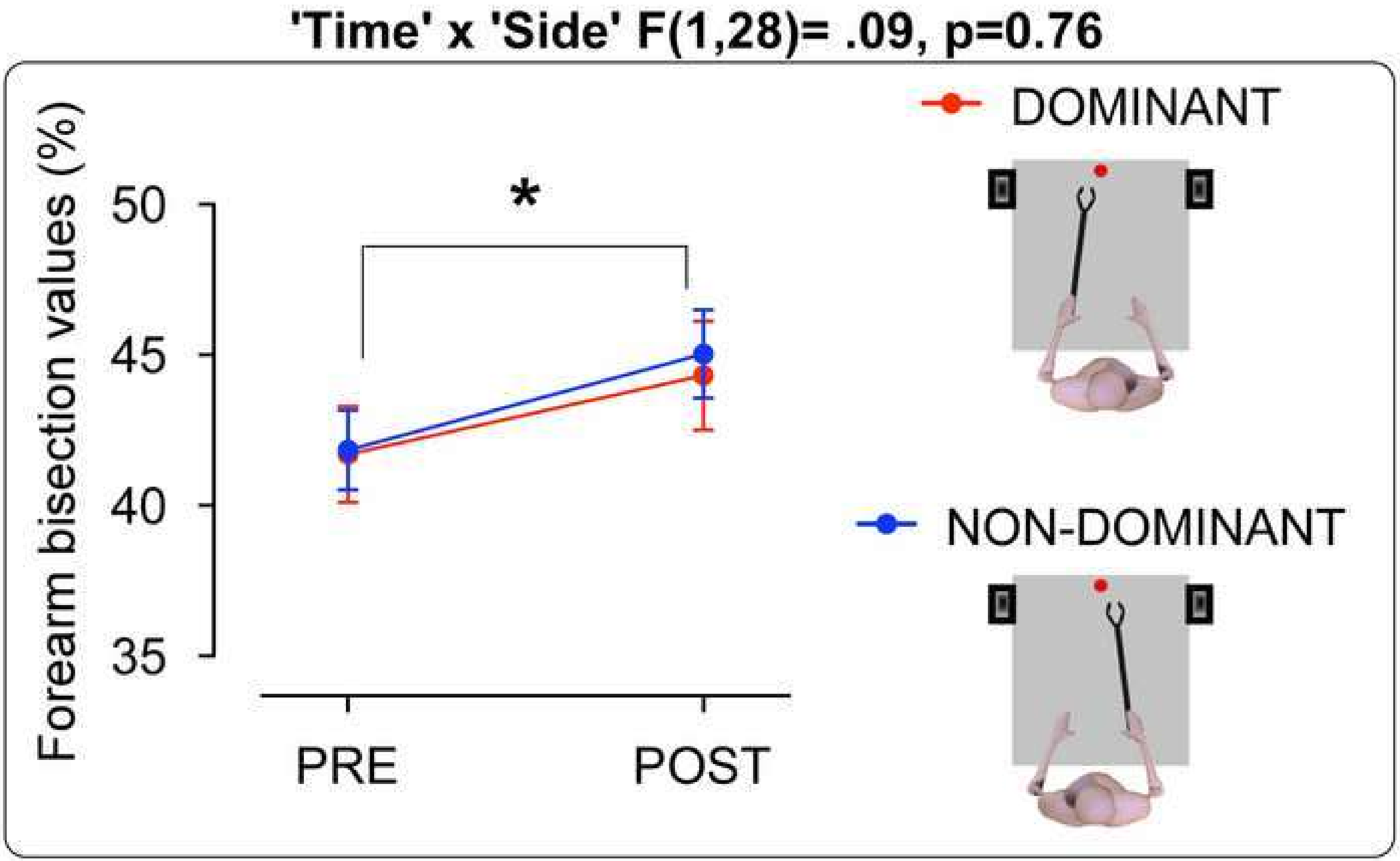
'Time' x 'Side' F(1,28)= .09, p=0.76
Forearm bisection values (%)
50
45
40
35
*
PRE
POST
DOMINANT
NON-DOMINANT

Figure 6

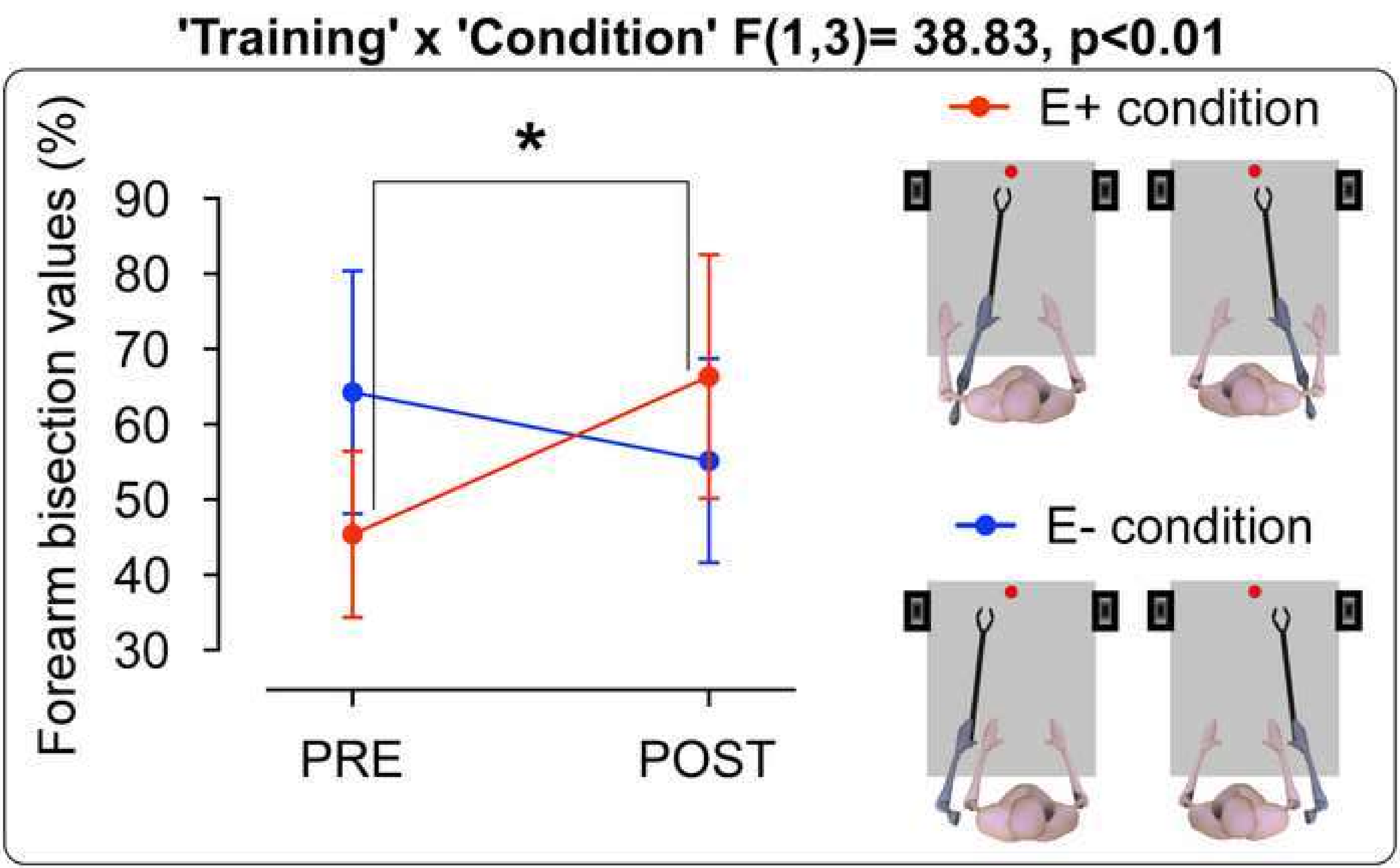
'Training' x 'Condition' F(1,3)= 38.83, p<0.01
Forearm bisection values (%)
90
80
70
60
50
40
30
*
PRE
POST
E+ condition
E- condition

Figure 7

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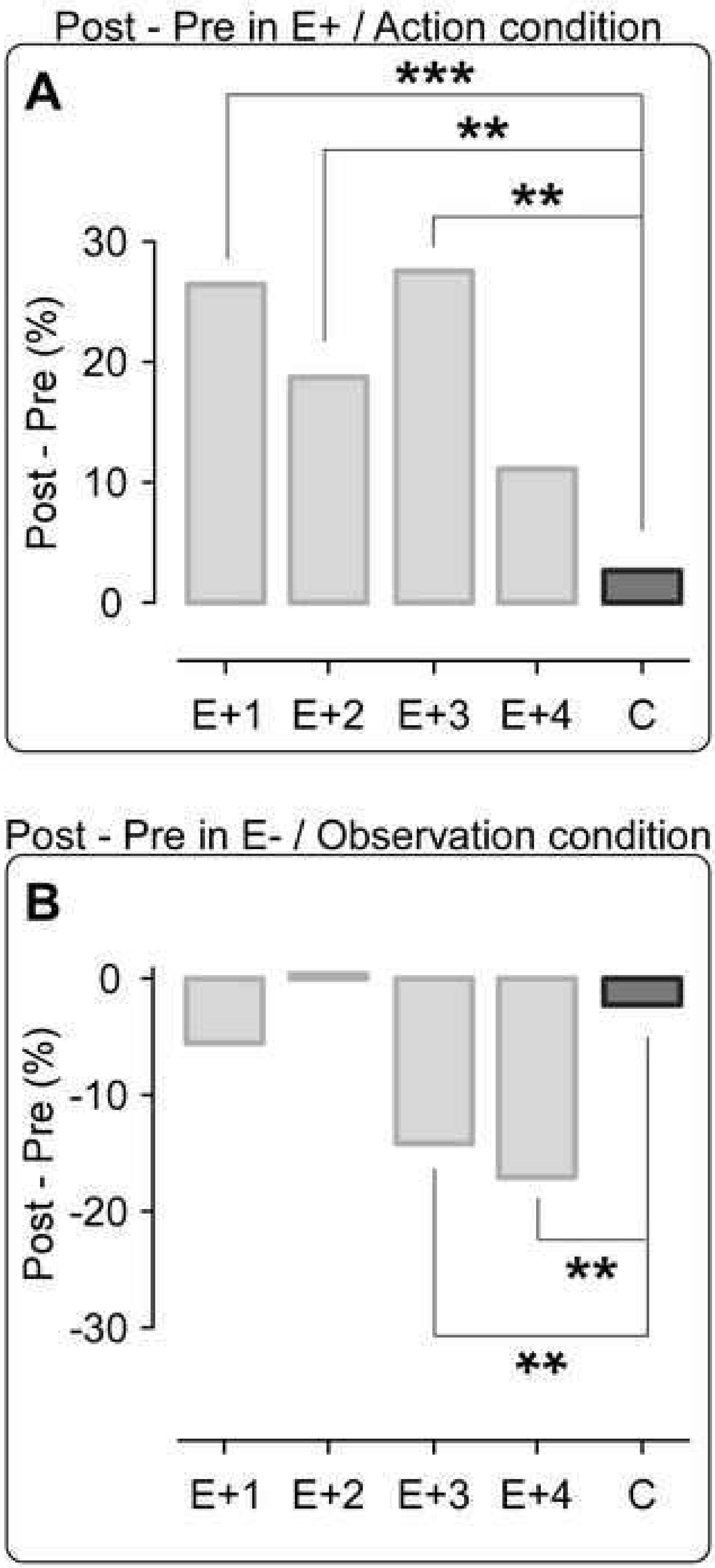

Video 1

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Video Still 1

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