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This is a pre print version of the following article:

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1662949 since 2018-06-19T15:47:23Z

Published version:

DOI:10.1016/j.cortex.2017.06.004

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09 January 2025

Feeling touch on the own hand restores the capacity to visually discriminate it from someone else' hand: pathological embodiment receding in brain-damage patients.

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Abstract

The sense of body ownership, i.e. the belief that a specific body part belongs to us, can be selectively impaired in brain-damaged patients. Recently, a pathological form of embodiment has been described in patients who, when the examiner's hand is located in a body-congruent position, systematically claim that it is their own hand (E+ patients). This paradoxical behavior suggests that, in these patients, the altered sense of body ownership also affects their capacity of visually discriminating the body-identity details of the own and the alien hand, even when both hands are clearly visible on the table. Here, we investigated whether, in E+ patients with spared tactile sensibility, a coherent body ownership could be restored by introducing a multisensory conflict between what the patients feel on the own hand and what they see on the alien hand. To this aim, we asked the patients to rate their sense of body ownership over the alien hand, either after segregated tactile stimulations of the own hand (out of view) and of the alien hand (visible) or after synchronous and asynchronous tactile stimulations of both hands, as in the rubber hand illusion set-up. Our results show that, when the tactile sensation perceived on the patient's own hand was in conflict with visual stimuli observed on the examiner's hand, E+ patients noticed the conflict and spontaneously described visual details of the (visible) examiner's hand (e.g. the fingers length, the nails shape, the skin color…), to conclude that it was not their own hand. These data represent the first evidence that, in E+ patients, an incongruent visual-tactile stimulation of the own and of the alien hand reduces, at least transitorily, the delusional body ownership over the alien hand, by restoring the access to the perceptual self-identity system, where visual body identity details are stored.

Keywords:

Brain-damaged Patients; Sense of Body Ownership; Body Awareness; Pathological Embodiment; Multisensory Conflict.

Acknowledgements: The authors are grateful to all of the patients and volunteers involved in the study. This work has been funded by MIUR-SIR 2014 grant (RBSI146V1D) and by the San Paolo Foundation 2016 grant (CSTO165140) to F.G.

1. Introduction

The sense of body ownership (i.e. the feeling that our different body parts belong to us; Blanke, Slater, & Serino, 2015; Gallagher, 2000) is something that we typically take for granted. However, experimental manipulations in healthy people, such as the rubber hand illusion (RHI) (Botvinick & Cohen, 1998), can temporarily alter the sense of body ownership. During the RHI, the subjects watch a lifelike rubber hand being touched while their own hand, hidden from view, is touched at the same time. This manipulation creates the disturbing *feeling* that the artificial hand is part of the own body, and the real hand can be somehow 'disembodied' (Della Gatta et al., 2016; Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008; Moseley et al., 2008), although subjects always *know* that the rubber hand *is not* part of their body. More dramatic body ownership alterations can be observed in pathological conditions (Brugger & Lenggenhager, 2014). Brain damage can disrupt the sense of body ownership and make patients convinced that one of their upper or lower limbs does not belong to them but to another person, as in the somatoparaphrenic syndrome (Bisiach, Meregalli, & Berti, 1990; Vallar & Ronchi, 2009). Recently, a complementary body awareness disorder has been described where brain-damaged patients claim that the examiner's hand is their own hand, whenever it is located in a body-congruent position. Because of this pathological embodiment, we named them E+ patients (Fossataro, Gindri, Mezzanato, Pia, & Garbarini, 2016; Garbarini et al., 2013, 2014, 2015; Garbarini & Pia, 2013; Pia, Garbarini, Fossataro, Burin, & Berti, 2016; Pia, Garbarini, Fossataro, Fornia, & Berti, 2013). In order to observe this phenomenon, the co-examiner's hand must be placed on the table next to the patient's contralesional affected hand, aligned with the patient's shoulder and, therefore, perceived in egocentric perspective. In this set-up, when the examiner asks the patient to identify his/her own affected hand, either by reaching with his/her intact hand or by naming a colored object in front of it, the patient systematically identifies the examiner's hand as his/her own. By contrast, pathological embodiment does not occur when the alien hand is misaligned with the patient's shoulder, when it is perceived in allocentric perspective or positioned in the intact ipsilesional body-side and when, instead of a human hand, a rubber hand is used. Considering the E+ patients' neurological characteristics, pathological embodiment seems to be strongly associated to severe primary sensory-motor deficits as well as to other cognitive deficits, such as neglect and personal neglect. However, none of these deficits alone can explain pathological embodiment because double dissociations between embodiment, neglect and primary sensory-motor deficits have been described (Garbarini, Pia, Fossataro, & Berti, in press). It is interesting to note that, the incidence of somatoparaphrenia in E+ patients is quite low. This, in turn, is consistent with the fact that this disease is rarely observed after the first week post-stroke (Vallar & Ronchi, 2009), whereas the pathological embodiment is reported in the sub-acute or chronic phase of the illness (Fossataro et al., 2016; Garbarini et al., 2013, 2014, 2015; Garbarini & Pia, 2013; Pia et al., 2016, 2013). However, when both the own and the alien hands are present and the examiner explicitly asks about their ownership, E+ patients not only misidentify the alien hand as their own, but also misattribute their own hand to the other person. In other words, E+ patients show, only in this condition, an explicit sense of disownership. The coexistence of the two delusional beliefs (i.e., disownership of the own hand and ownership of an alien hand) in the same patient, suggests that these two forms of body delusion might share at least some features. Accordingly, a previous study investigating the relationship between asomatognosia and RHI in stroke patients suggested that a number of asomatognosic patients, with impairment of the ability to perceive their real hand as belonging to them, easily integrated the fake hand as their own (Zeller, Gross, Bartsch, Johansen-Berg, & Classen, 2011).

One of the most counterintuitive observations related to E+ patients' behavior is that pathological embodiment occurs not only with a static alien hand, but also when the alien hand moves or when it is touched. Indeed, when E+ patients observe the examiner's hand reaching for an object or being stimulated, they experience to move their own hand (Fossataro et al., 2016; Garbarini et al., 2013, 2015) or to feel tactile sensations on it (Fossataro et al., 2016; Garbarini et al., 2014; Pia et al., 2013). With respect to the motor domain, it is interesting to note that E+ patients with contralesional hemiplegia are usually aware of their motor deficits and, when they are asked to move their affected hand, they perfectly know that they cannot perform any movement (i.e. they are not anosognosic). Thus, we could expect that, when the alien hand moves, the pathological embodiment would recede and patients would correctly recognize that the moving hand is the examiner's hand and not their own. On the contrary, what we found is that, when the alien hand moves, E+ patients claim they are moving their own (paralyzed) hand (Fossataro et al., 2016; Garbarini et al., 2013, 2015). This suggests the presence of a top-down control of the sense of body ownership on motor awareness.

When E+ patients are not in the embodiment condition, they are aware of their motor impairment, whereas when body awareness is affected by the experimental manipulation, then they seem to feel that their left (paralyzed) hand moves. Interestingly, other aspects of motor cognition are affected by the sense of body ownership such as the sense of agency because E+ patients ascribed the alien hand's movements to themselves (Fossataro et al., 2016; Garbarini et al., 2013, 2015).

With respect to the sensory domain, it is important to note that E+ cases with spared tactile sensibility on both hands have been described (Fossataro et al., 2016; Garbarini et al., 2014; Pia et al., 2013). In these cases, we could expect that, when the patients observe the alien hand being stimulated without receiving tactile stimuli on their own hand, the pathological embodiment would recede and the patients would correctly recognize that the stimulated hand was the examiner's hand and not their own. On the contrary, what we found is that, when E+ patients observe the alien hand being touched, they report to feel tactile sensation on their own hand (Garbarini et al., 2014; Pia et al., 2013). It is important to note that the tactile sensation on the alien hand is reported either when they had intact tactile sensibility on the own hand [a few cases with spared tactile sensibility have been described (Fossataro et al., 2016; Garbarini et al., 2014; Pia et al., 2013)] or when the own hand is affected by tactile anesthesia but they do not acknowledge the sensory deficit [anosognosia for hemianaesthesia; see (Pia, Spinazzola, et al., 2014; Pia, Cavallo, & Garbarini, 2014)]. On the other hand, when patients are aware that they cannot feel any tactile stimulation on the own hand (hemianaesthesia without anosognosia), they did not report to experience any tactile stimuli on the alien hand. These observations suggest that the belief the patients have, not only about their body, but also about their sensory abilities (whether true or false) is transferred to the alien hand, once it is embodied (Pia et al., 2013). This means that this delusion of body ownership meets the criteria of a recently proposed definition of the embodiment concept, claiming that others' body parts can be considered as fully embodied, "if and only if", as in these patients, "some properties of them are processed in the same way as the properties of one's own body" (De Vignemont, 2011).

In the present paper, we asked whether, and to what extent, this altered sense of body ownership, exerting top-down modulation on sensory perception, can be contrasted by a bottom-up multisensory conflict between what the patients feel on the own hand and what the patients see on the alien hand, restoring a coherent sense of self (Gentile, Guterstam, Brozzoli, & Ehrsson, 2013). To this aim, three rare cases of E+ patients with spared tactile sensibility on the contralesional body parts were selected. Together with two control groups (E- patients with similar neurological/neuropsychological characteristics and age-matched healthy subjects), they took part in two experiments. In both experiments, the examiner's hand (i.e. alien hand) was always visible on the table while the patient's hand was hidden from view (as in the RHI set-up). Patients were asked to rate their sense of body ownership over the alien hand, either after segregated tactile stimulations of the own hand (out of view) and of the alien hand (visible on the table) (Experiment 1) or after synchronous and asynchronous tactile stimulations of both hands, as in the RHI set-up (Experiment 2). See details in section 2.2 and in Figure 1A and 1B. In Experiment 1, we hypostasized that to feel a touch on the (hidden) own hand, while the alien (visible) hand is not touched, should create a multisensory conflict that may reduce (or even cancel) the pathological embodiment over the alien hand. In Experiment 2, we hypostasized that, in the asynchronous condition, where both hands are stimulated but with a temporal difference, the strength of the pathological embodiment might be reduced.

2. Materials and methods

2.1 Patients' recruitment and participants

Six brain-damaged patients of cerebrovascular origin, with contralesional upper limb sensory-motor deficits, were recruited at the "San Camillo" Hospital (Turin, Italy). Exclusion criteria were: 1) previous neurological or psychiatric history; 2) severe general cognitive impairment [i.e. patients under the MOCA cut off were excluded (Bosco et al., 2017)]; 3) visual field deficits (i.e. patients with hemianopia were excluded); 4) tactile deficits [i.e. we included patients without hemianaesthesia (AH=0) or patients with tactile extinction (i.e. omission of the left contralesional stimulus during bilateral stimulation) who showed spared tactile sensibility when unilateral tactile stimuli were delivered to the left hand (AH=1) (Pia, Spinazzola, et al., 2014; Pia, Cavallo, et al., 2014)]. All patients were assessed using common neuropsychological tests: see demographic details and neurological/neuropsychological assessment results in Table 1.

--- Table 1 about here ---

In order to include patients in the experimental or in the control group, we tested them with an ad hoc protocol devised to assess the presence/absence of pathological embodiment, proposed in previous studies (Fossataro et al., 2016; Garbarini et al., 2013, 2014, 2015; Garbarini & Pia, 2013; Pia et al., 2013). According to this evaluation, patients were classified as E+ or E- patients. Three out of six patients were assigned to the E+ patients group (mean age ± standard deviation= 75.66±3.05) and the others three to the E- patients group (mean age ± standard deviation= 75.33±9.02). Note that, in this first evaluation, we also used additional trials in which a rubber hand was used instead of the examiner's hand. According to previous studies (Pia et al., 2013), when the rubber hand was used, the pathological embodiment did not occur. Thus, in the experimental procedures (see section 2.2), we always used the co-examiner's hand.

Ten aged-matched healthy subjects (6 females, mean age ± standard deviation: 69.7±13.34) were enrolled in the study as healthy control group. All participants were naive to the experimental procedure and to the aim of the research and provide written informed consent to participate in the study. In accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194), all the experimental procedures were approved by the Ethical Committee of the ASL TO 1 of Turin (protocol number 46485/13).

2.2 Experimental procedure

We employed a black wooden box (60x40x5 cm) divided in two equal parts (30x30x20 cm) by a panel. One of the two parts was open to the view in order to allow viewing the other's hand (stimulated or not, according to the experimental condition), while the other half has to take out of sight the real subject's hand. Two square holes (12x12 cm) on either horizontal sides of the box allowed placing both the participant's arm and the experimenter's arm (i.e. alien hand). A black towel covered the subject's shoulders and the proximal end of both the subject's real hand and the alien hand, so that the alien hand was perceived as an extension of the participant's own left hand and arm. The box was placed in front of the subject's chest (about 15 cm far) and set in order to have the other's hand, placed in the half of the box open to the view, aligned with the participant's left shoulder. Before starting, participants were familiarized with the setting, and instructed to all procedures and rating scales. The participants' left arm was placed within the part of the box hidden to the view, the palm was facing down and the fingers were stretched out. In the other half of the box, open to the view, the co-experimenter's left hand (i.e. alien hand) was placed (at a distance of approximately 25 cm from the own hand), exactly where the subject's hand has to be. During each experimental condition, participants were asked to look carefully at the alien hand in the half of the box open to the view. See Figure 1.

--- Figure 1 about here ---

2.2.1. Experiment 1

Participants underwent two different conditions, in which they were asked to carefully watch the alien hand, placed in a congruent position with respect to their body, while their own hand (the contralesional affected hand in patients) was always out of view. In the first condition, tactile stimuli were delivered to the alien hand (Alien condition) while in the second condition stimuli were delivered to the own hand (Own condition). Each stimulation lasted about 180 s. See Figure 1A. All participants underwent both conditions and the order of conditions was randomized between subjects. In both conditions, at the end of the stimulation procedure, participants were asked to rate their agreement with respect to both Ownership and Sensation statement (see section 2.3).

2.2.2. Experiment 2

Participants underwent the classical RHI conditions in which they were asked to carefully watch the alien hand, placed in a congruent position with respect to their body, while their own hand (the contralesional affected hand in patients) was always out of view. The participants' own hand could be c) synchronously stroked with the alien hand, (Synchronous condition) or d) asynchronously stroked with alien hand (Asynchronous condition). Each stimulation lasted about 180 s. All participants underwent all conditions, which were counterbalanced between subjects. See Figure

1B. Note that, differently from the classical RHI paradigm we did not use a rubber hand but a real human hand (the co-examiner's one). As mentioned above, the rubber hand is not able to induce the pathological embodiment and here we were interested in evaluating the embodiment persistence/receding, depending on the conditions. Note also that the proprioceptive drift measure, usually employed during the RHI, was not employed here because of the proprioceptive deficit shown by E+ patients. Due to this deficit, they were not able to perform the task at the baseline, pre-stimulation condition.

2.3 Self report measures

In both experiments, at the end of each stimulation condition, participants were asked to rate on a 0-10 Likert scale their agreement/disagreement with respect to two *ad hoc* statements, concerning both the tactile sensation and the sense of ownership over the alien hand (as in Bucchioni et al., 2016). Sensation statement: *"I felt the tactile sensation coming from the hand I was looking at"*. Ownership statement: *"I felt as mine the hand I was looking at"*. The Likert scale was ranking from 0 (i.e. *I don't agree at all*) to 10 (i.e. *I totally agree*). Note that, in the clinical evaluation, in order to assess the presence/absence of pathological embodiment, patients were asked to answer to yes/no questions (Fossataro et al., 2016; Garbarini et al., 2013, 2014, 2015; Garbarini & Pia, 2013; Pia et al., 2013). However, during the experimental phases, in order to quantify the expected embodiment receding and to compare the patients' and the controls' responses, participants were asked to rate their sense of body ownership on a Likert scale.

2.4 Data analysis

In both Experiment 1 and Experiment 2, similar analyses were performed. With respect to the healthy controls data, we first assessed for the normal distribution of the residual by means of the Shapiro-Wilk Test. Since the residuals were not normally distributed ($p<0.05$), the Wilcoxon signed-rank test for pairwise comparisons (two tailed) was used for both Sensation and Ownership statement separately, in order to compare the subjective ratings of the two experimental conditions (Experiment 1: Alien vs Own; Experiment 2: Synchronous vs Asynchronous). For each test performed, we reported mean, standard deviation, Z, p and *r* value [calculated manually by dividing the Z value by the squared-root of the total sample size (Rosenthal, 1994)]. With respect to E- patients and E+ patients, given the small number of cases (i.e. three patients for each group), we performed a between groups analysis by means of a Crawford test (one tailed), specifically devised to test differential deficits exhibited by clinical sample on two different test. "It does this by applying William's test for non-independent correlations (Williams, 1959): the correlation between group membership (clinical versus control) and Test A is compared with the correlation of group membership and Test B. Computing a correlation between group membership and a variable is equivalent to running a t-test or one-way ANOVA comparing the control and patient samples on the variables" (Crawford, Blackmore, Lamb, & Simpson, 2000). Thus, correlations between group membership (E+, E- patients or control) and scores on both test A (i.e. Alien condition in Experiment 1; Synchronous condition in Experiment 2) and test B (i.e. Own condition in Experiment 1; Asynchronous condition in Experiment 2) were computed and entered in the analysis.

Finally, in order to compare the presence/absence of the embodiment phenomenon between each E+ patient and both healthy subjects and E- groups, the subjective ratings were entered in a Crawford's test (one tailed) specifically devised to test whether an individual's score is significantly different from a control or normative sample. "It provides a point and interval estimate of the abnormality of the case's score, i.e. it estimates the percentage of the population that would obtain a lower score (together with a 95% confidence interval on this percentage)" (Crawford, Garthwaite, & Porter, 2010).

3. Results

3.1 Experiment 1

In healthy controls group, Wilcoxon test, at both Ownership and Sensation statement, does not showed a significant difference between Own and Alien condition [mean ± standard deviation; Ownership statement: Alien= 0.6±1.57; Own= 2.3±3.88; Z=1.278019; p= 0.20; *r*=0.40; Sensation statement: Alien= 0.8±1.3; Own= 1.3±3.19; Z=0.13484; p= 0.89; *r*= 0.04). This means that healthy subjects gave similarly low ratings in both conditions, suggesting that segregated stimulations of the own and the alien hand do not modulate the sense of body ownership. See Figure 2.

Between E- patients and healthy subjects group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there are no differences in groups performances. At the Ownership statement, the correlation between group membership and score on the Alien condition (-0.106) was comparable to the correlation between group membership and the score on the Own condition (-0.06), [$t(10) = -0.085$; $p = 0.46$]. At the Sensation statement, the correlation between group membership and score on the Alien condition (-0.213) was comparable to the correlation between group membership and the score on the Own condition (0.20), [$t(10) = -0.856$; $p = 0.21$]. Crucially, between E+ patients and E- patients group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there was a significant difference in groups performances. At the Ownership statement, the correlation between group membership and score on the Alien condition (0.991) was significantly greater than the correlation between group membership and the score on the Own condition (-0.192), [$t(3) = 3.229$; $p = 0.02$]. At the Sensation statement, the correlation between group membership and score on the Alien condition (0.996) was significantly greater than the correlation between group membership and the score on the Own condition (-0.48), [$t(3) = 3.386$; $p = 0.02$]. Finally, between E+ patients and healthy subjects group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there was a significant difference in groups performances. At the Ownership statement, the correlation between group membership and score on the Alien condition (0.802) was significantly greater than the correlation between group membership and the score on the Own condition (-0.149), [$t(10) = 2.77$; $p = 0.01$]. At the Sensation statement, the correlation between group membership and score on the Alien condition (0.769) was significantly greater than the correlation between group membership and the score on the Own condition (-0.085), [$t(10) = 2.104$; $p = 0.03$]. Thus, this suggests that only E+ patients group, due to the pathological embodiment, gave significantly greater scores in the Alien condition (mean ± standard deviation, Ownership= 9 ± 1; Sensation= 8.3 ± 0.57), than to the Own condition (mean ± standard deviation, Ownership=

1.06±1.67; Sensation= 0.06±0.05) showing an embodiment persistence in the Alien condition and crucially, an embodiment receding in the Own condition. See Figure 2.

--- Figure 2 about here ---

For both Ownership and Sensation statement, Crawford's tests (one tailed) for single-subject analysis (Crawford et al., 2010), showed that in the Alien condition there is a significant difference between each E+ patient's ratings and the ratings of both healthy subjects group (mean ± standard deviation, Ownership= 0.6±1.57; Sensation= 1.3±3.19) and E- patients group (mean ± standard deviation, Ownership= 0.26±0.25; Sensation= 0.1±0.1). This suggests that, in this condition, only E+ patients gave high ratings (E+1: Ownership= 8; Sensation=8; E+2: Ownership= 10; Sensation= 9; E+3: Ownership= 9; Sensation= 8) due to the pathological embodiment persistence ($p< 0.005$ for each comparison; see Figure 2). Crucially, no difference between each E+ patients and both E- patients group and healthy subjects group was found in the Own condition ($p> 0.05$ for each comparison; see Figure 2), showing that, in this condition, all three E+ patients, due to the pathological embodiment receding, gave low ratings (E+1: Ownership= 0; Sensation=0; E+2: Ownership= 3; Sensation= 0; E+3: Ownership= 0; Sensation= 0) comparable to those given by the control groups (mean ± standard deviation, E- patients: Ownership= 1.8±2.77; Sensation= 2.9±4.42; healthy subjects: Ownership= 2.3±3.88; Sensation= 0.8±1.61). Single-subject analysis results are reported in Table 2.

--- Table 2 about here ---

3.2 Experiment 2

In healthy controls group, Wilcoxon test, at both Ownership and Sensation statement, showed a significant difference between the Synchronous and the Asynchronous condition [mean ± standard deviation; Ownership statement: Synchronous= 5.22±3.93; Asynchronous= 1±1.88; Z= 2.66557; $p= 0.007$; $r= 0.84$; Sensation statement:

Synchronous= 4.62±3.55; Asynchronous= 0.62±1.55; Z= 2.66557; p= 0.007; *r*= 0.84). In healthy subjects, this result mirrors the classical RHI effect with higher ratings for the Synchronous condition compared to the Asynchronous condition. See Figure 3.

Between E- patients and healthy subjects group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there were no differences in groups performances. At the Ownership statement, the correlation between group membership and score on the Synchronous condition (0.051) was comparable to the correlation between group membership and the score on the Asynchronous condition (-0.192), [t(10)= 0.825; p= 0.21]. At the Sensation statement, the correlation between group membership and score on the Synchronous condition (0.379) was comparable to the correlation between group membership and the score on the Asynchronous condition (0.438), [t(10)= -0.223; p= 0.41]. Crucially, between E+ patients and E- patients group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there were no differences in groups performances. At the Ownership statement, the correlation between group membership and score on the Synchronous condition (0.613) was comparable to the correlation between group membership and the score on the Asynchronous condition (0.746), [t(3)= -0.317; p= 0.38]. At the Sensation statement, the correlation between group membership and score on the Synchronous condition (0.204) was comparable to the correlation between group membership and the score on the Asynchronous condition (-0.027), [t(3)= 0.482; p= 0.33]. Finally, between E+ patients and healthy subjects group, Crawford test for differential deficits in pathological sample (Crawford et al., 2000) showed that, at both Ownership and Sensation statement, there were no differences in groups performances. At the Ownership statement, the correlation between group membership and score on the Synchronous condition (0.398) was comparable to the correlation between group membership and the score on the Asynchronous condition (0.579), [t(10)= -0.677; p= 0.25]. At the Sensation statement, the correlation between group membership and score on the Synchronous condition (0.482) was comparable to the correlation between group membership and the score on the Asynchronous condition (0.386), [t(10)= 0.376; p= 0.35]. Thus, in E+ patients group, these results suggest an embodiment persistence in the Synchronous condition (mean ± standard deviation= 8.33±1.15) and crucially, an embodiment receding in the Asynchronous condition (mean ± standard deviation= 3.33±4.93). See Figure 3.

--- Figure 3 about here ---

For both Ownership and Sensation statement single-subject analysis (see Table 3), performed by means of Crawford's tests (one tailed), showed that, in Synchronous condition, no difference was found between each E+ patients and both E- patients and healthy subjects, either for the Ownership or for Sensation statement ($p > 0.05$ for each comparison; see Figure 3). In the Asynchronous condition, for both the Sensation and Ownership statement, different results were found depending on each patient. Patient E+1, both at Sensation and Ownership statement, gave high ratings (Ownership: 9; Sensation: 9), significantly different compared to the low ratings given by both E- patients (mean ± standard deviation, Ownership= 0.26±0.38; Sensation= 3.56±5.57) and healthy subjects (mean ± standard deviation, Ownership= 1±1.88; Sensation= 0.62±1.55) ($p < 0.05$ for each comparison; see Figure 3). On the contrary, patient E+2, both at Sensation and Ownership statement, gave low ratings (Ownership= 1; Sensation= 1), comparable to those given by both E- patients and healthy subjects ($p > 0.05$ for each comparison; see Figure 3). Finally, patient E+3, at the Ownership statement, gave high ratings (Ownership: 10) significantly different compared to the low ratings given by both E- patients and healthy subjects ($p < 0.05$ for each comparison; see Figure 3). By contrast, patient E+3, at the Sensation statement, gave low ratings (sensation: 0), comparable to those given by both E- patients and healthy subjects ($p > 0.05$ for each comparison; see Figure 3). Single-subject analysis results are reported in Table 3.

--- Table 3 about here ---

4. Discussion

When patients with pathological embodiment (E+ patients) look at the examiner's hand, located in a body-congruent position, systematically claim that that hand is their own. In the present study, we asked whether, in E+ patients with spared tactile sensibility, a coherent body awareness can be restored, when a multisensory conflict between what the patients feel on the own hand and what they see on the alien hand is introduced (Gentile et al., 2013). Indeed, we found that, when tactile sensations did not coincide with the visual feedback, that is when the tactile stimuli were delivered on the hidden own hand and not on the visible examiner's hand, the pathological embodiment receded.

In Experiment 1, our results showed, both in healthy subjects and in E- patients, that separated tactile stimulations of the own and the alien hand did not modulate the participants' sense of body ownership. Although some studies suggest that a modulation of the body ownership can be obtained in normal subjects by the sole vision of the fake hands being touched (Ferri, Chiarelli, Merla, Gallese, & Costantini, 2013; Holmes, Snijders, & Spence, 2006), our control groups were not affected by this stimulation. On the contrary, in E+ patients, the already altered sense of body ownership was modulated by the experimental conditions. When E+ patients observed the alien hand being touched without receiving any tactile stimuli on their own hand (Alien condition), the pathological embodiment was maintained whereas, when E+ patients perceived tactile stimuli on their own hand without observing any tactile stimuli on the alien hand (Own condition), the pathological embodiment receded. It is interesting to note that the behavior shown in the Alien condition resembles mirror-touch synesthesia, where people can experience tactile sensations in a given body part simply by looking at another person being touched on the same part. This might be due to an atypical functioning of the mirror-touch system (Blakemore, Bristow, Bird, Frith, & Ward, 2005). It has been also proposed that, in synesthetic people, the abnormal sensory feelings are accompanied by an alteration of the self-other discrimination system (for a review Banissy & Ward, 2013). This alteration does not lead to an actual misattribution of the other people body parts to the own body, as in E+ patients. However, a greater illusory experience, compared to healthy controls, has been described in synesthetic subjects during different experimental manipulations of body ownership (Aimola Davies & White, 2013; Maister, Banissy, & Tsakiris, 2013). In E+ patients, body ownership might exert a top-down modulation on visuo-tactile bimodal neurons in somatosensory cortex, known to be activated by vision through a mirror-like mechanisms, when subjects observe other bodies being touched (Bonini, 2016; Ishida, Nakajima, Inase, & Murata, 2009; Keysers & Gazzola, 2009). Normal body ownership, in order to discriminate between self and other's body, either up-regulates the somatosensory cortical activity, in order to bind conscious experience to the own body, or down-regulates the cortical activity, in order to avoid conscious experience for the events occurring on the others' bodies. On the contrary, in E+ patients, pathological body ownership, no longer able to discriminate between oneself and another body, can only up-regulate the somatosensory cortical activity, binding conscious tactile experience to both oneself and the other's body (Garbarini et al., in press). Indeed, the sense of ownership reported by E+ patients over the alien hand is not something that they just believe, but is more than just a mere judgment. It is something that they report to feel as own body (De Vignemont, 2011).

The above described results of the Alien condition confirm similar findings in our previous studies (Fossataro et al., 2016; Garbarini et al., 2014; Pia et al., 2013). In the present research, novel findings show that, when E+ patients perceived tactile stimuli on their own hand without observing any tactile stimuli on the alien hand, the pathological embodiment receded (lower ratings at the Ownership statement) as well as the corresponding tactile sensation (lower ratings at the Sensation statement). How can we explain this embodiment receding? Body ownership is an inherently multimodal concept, since all senses together contribute to build a coherent body representation (Blanke, 2012; Blanke et al., 2015). However, when somatosensory inputs are lost, as after brain damage, a residual capacity to discriminate between self and others' body can rely only on visual inputs. Indeed, we have observed E- cases with severe motor, tactile and proprioceptive deficits, who immediately discriminate between the own and the alien hand referring to different visual details [the color of the skin, the shape, the age, the dimension of the hand]. These visual-identity details resemble the concept of *"body image"* which represents the perceived form of our body, in terms of its size, shape, and distinctive characteristics (Gallagher, 1986), or the more recently proposed concept of "*somatoperception",* which refers to the essentially perceptual process of constructing perceptual representations of the body and somatic stimuli from perceptual input (Longo, Azãnón, & Haggard, 2010). These visual-identity details are stored in what we call a "perceptual self-identity system" (Garbarini et al., in press), that allows, when spared as in E- patients, to discriminate between self and others' body. On the contrary, E+ patients, where the lesion must have damaged the possibility to directly access the perceptual self-identity system, are not able to utilize visual details to discriminate between the own and the alien hand and base their ownership judgment on a pre-existing knowledge of body structure (pre-existing body representation), that does not include updated details of the body self. Thus, in E+ patients, each stimulus matching the constraints of this pre-existing body representation (e.g. a human hand, aligned with the patients' shoulder and perceived in egocentric perspective) is felt as part of the patient's own body [i.e. it is embodied, (De Vignemont, 2011)].

However, when E+ patients have a spared somatosensory system, this can be activated by the tactile stimulation received on the own hand, and this may be sufficient to immediately access the perceptual identity system and therefore become aware of the visual self/other identity details previously ignored. Indeed, during the Own condition, while perceiving tactile stimuli on their own hand and observing the alien not-stimulated hand, all three E+ patients noticed the visuo-tactile conflict, spontaneously naming several details of the examiners' hand (e.g. the fingers length, the nails shape, the skin color…) and concluding that the alien hand was not their own hand.

Interestingly, in normal subjects, the experimentally induced modulation of ownership during the RHI has been shown to enhance the perceived physical similarity between self and other body [i.e. normal subjects experiencing the RHI perceived their hand and the rubber hand as significantly more similar in terms of their physical appearance (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2009)]. Coherently, during the RHI, an increase of the functional connectivity between posterior visual-related areas, involved in body part recognition (i.e. lateral occipitotemporal cortex –LOC and extrastriate body area - EBA), and anterior brain areas involved in multisensory integration (i.e. premotor cortex, PMC), was found to be stronger in the "re-calibration phase" before illusion onset (Limanowski & Blankenburg, 2015). According to a recent model of "prediction error minimization" during the RHI (Apps & Tsakiris, 2014), this increased fronto-occipital functional connectivity, conveyed to parietal regions, presumably resolves the conflict associated to sensory input during the illusion, such as the discrepancy in visual appearance between real and rubber hand. Interestingly, a recent time-frequency EEG study of the RHI (Kanayama, Morandi, Hiraki, & Pavani, 2016), showed that, during synchronous visuo-tactile stimulation, an altered causal relationship from the medial frontal to the parietal regions transitorily unlocks the mechanisms that preserve body integrity, allowing RHI to emerge. Interestingly, the lesion pattern of the three E+ patients here (see Table 4) is compatible with previous studies on E+ patients (Fossataro et al., 2016; Garbarini et al., 2015), showing a main involvement of the white matter tracts connecting frontal to posterior areas of the brain (i.e. the superior longitudinal fasciculus is one of the most frequent finding associated to pathological embodiment). Thus, a damaged connectivity between frontal and posterior visual-related areas, such as EBA and LOC, can potentially explain the E+ patients' deficit in accessing the body visual details stored in the perceptual self-identity system.

--- Table 4 about here ---

We can speculate that, in the three E+ cases described here, during the stimulation of the own hand, the online activity of the spared somatosensory system can force the connection with the visual areas where the information related to the body self-details are stored, thus producing the (transitory) embodiment receding. Within the framework provided by predictive coding, it has been suggested that RHI emerges through attenuation of somatosensory precision. For instance, touch-evoked potentials, elicited by brush-strokes, were selectively attenuated during the RHI (Zeller, Litvak, Friston, & Classen, 2014). Coherently, the intrinsic connectivity in the primary somatosensory area (S1) was significantly attenuated during the illusion perception due to a top-down modulation exerted by PMC (Zeller, Friston, & Classen, 2016). If, during the RHI, in order for the embodiment to occur, the somatosensory system has to be down-regulated, it makes sense that, in E+ patients, in order for the embodiment to recede, the (spared) somatosensory system has to be up-regulated. Thus, the stimulation in the Own condition, may produce a reverse RHI effect, enhancing the somatosensory precision and unveiling the conflict between the patient's and the examiner's hand.

In Experiment 2, for both Ownership and Sensation statement, all three groups gave higher ratings in the Synchronous than the Asynchronous condition. In healthy subjects and in E- patients, this result mirrors the classical RHI effect (Botvinick & Cohen, 1998; Burin et al., 2015; Della Gatta et al., 2016; Ehrsson, Spence, & Passingham, 2004; Moseley et al., 2008; Tsakiris, 2010; Tsakiris & Haggard, 2005). In E+ patients, sensory manipulations similar to the ones used to induce RHI in normal subjects, maintain embodiment of the alien hand in Synchronous condition. In the Asynchronous condition, known to prevent the embodiment of the rubber hand during the RHI, the group analysis showed a receding of pathological embodiment similar to that found in Experiment 1. However, in single-subject analysis, we found different results depending on the patient. In particular, an embodiment receding was present, according to the Sensation statement, in two out of three patients (E+2 and E+3) and, according to the Ownership statement, only in one patient (E+2). In other words, the stimulation in the Asynchronous condition obtains less reliable results that the manipulation of Experiment 1. This may not be so surprising if we consider the important difference between the conditions of the two experiments. Indeed, in the first experiment, when tactile stimulations were segregated, the contradiction between what the patients felt on the own hand and what the patients saw on the alien hand was sufficient to counteract the embodiment attitude. In the second experiment, although the Asynchronous condition introduced a temporal delay between two tactile stimulations (on the own and on the alien hand), both hands were touched (although in slightly different moments). When the touch was delivered on the own hidden hand, this resembled the Own condition of Experiment 1, possibly pressing towards a receding from the embodiment. However, immediately after that, another touch was delivered on the visible alien hand, triggering the typical embodiment condition. Therefore, in the Asynchronous condition, two conflicting stimulations may have caused the variability of patients' responses, depending on which of the two stimulations prevails.

It is important to note that the embodiment phenomena observed in E+ patients in the Synchronous condition and in the RHI in normal subjects have important similarities and crucial differences. On one hand, pathological embodiment relies on similar constraints as those present in the RHI. It has been demonstrated that the RHI does not arise when the fake hand is placed in allocentric perspective or in a non-compatible posture, or when it is replaced by a neutral object (Costantini & Haggard, 2007; Ehrsson et al., 2004; Tsakiris & Haggard, 2005). Similar constraints characterize the pathological embodiment observed in E+ patients, which occurs only when the alien hand is aligned with the patients' shoulder and perceived in egocentric perspective congruently with the patient's body. This means that to meet postural constrains is a necessary pre-requisite to induce the embodiment. On the other hand, there are several differences between the altered body ownership during the RHI and the abnormal body ownership in E+ patients. First of all, the RHI is obtained with a prosthetic, human-like, plastic hand while in E+ patients, only a real human hand is able to induce the pathological embodiment, suggesting that a pre-existing distinction between biological and artificial categories (Kriegeskorte et al., 2008; Mazzoni, Brunel, Cavallari, Logothetis, & Panzeri, 2011) is spared in our patients. Thus, while the RHI studies point out the human-like appearance as a necessary constraint for inducing the embodiment, the E+ patients' studies suggest that also a biological constraint plays an important role in the construction of body ownership. Accordingly, it has been described a somatoparaphrenic patient who, during the self-touch stimulations, achieved ownership over the own (previously disembodied) arm and over different foreign arms (including both human and rubber hand), but the stroking time that was needed to achieve the sense of ownership was longer for the rubber hand compared to the human hand (van Stralen, van Zandvoort, & Dijkerman, 2011). Second, in E+ patients, pathological embodiment is a consequence of brain lesions and it is spontaneous and not induced by an experimental procedure that manipulates different sources of stimulation. In other words, differently from the RHI, no concurrent tactile stimuli are necessary, but the simple vision of the alien hand induces pathological embodiment in E+ patients. Third, while in the RHI subjects always know that the rubber hand is not their real hand, in the E+ condition, patients actually believe that the alien hand belongs to themselves. In other words, the embodiment phenomenon is qualitatively different from the illusion experienced during the RHI and represents a completely altered subjective feeling of body self. For this reason, we usually employed "yes or no" answers to detect the presence/absence of the delusion instead of subjective ratings on a Likert scale, as during the RHI procedure. However, when a Likert scale was used, as in the present study, we noticed that, while healthy subjects gave ratings distributed through all the Likert scale, E+ patients' ratings had a bimodal distribution, with responses centered at the two extremities of the scale (as if they were giving yes or no answer).

5. Conclusion

Previous studies demonstrated that experimental procedures inducing a multisensory conflict between touch and vision have been satisfactorily applied in clinical rehabilitation contexts. Indeed, cross modal illusions, such as the mirror box illusion and the RHI, seem to be useful in restoring, at least in part, disorders of body representation related to pain, sensory, and motor impairments in neuropsychological and neurological diseases (Bolognini, Russo, & Vallar, 2015). The present findings represent the first evidence that, in E+ patients with spared tactile sensibility, a multisensory conflict between what the patients feel on the own hand and what they observe on the alien hand reduces, at least transitorily, the delusional body ownership over the alien hand, by restoring the access to a perceptual self-identity system, where visual body identity details are stored. This, in turn, suggests that a spared bottom-up mechanism, such as the processing of tactile stimuli, may modulate a top-down process, such as the sense of body ownership, by restoring an effective connection with visual areas containing information related to the visual details of the body self.

Patients' neuropsychological assessment	E+1	E+2	E+3	E-1	E-2	E-3
Sex	F	F	F	M	M	M
Age	73	75	79	66	84	76
General cognitive impairment	24.5	19.7	17	24	22	21
Visual Field Defect	0-0	0-0	0-0	0-0	0-0	0-0
Hemiplegia (HP)	1	3	0	2	3	0
Hemianaesthesia (HA)	1	0	1	1	0	0
Anosognosia for HP	/	0	/	0	/	/
Proprioception	+	+	+	+	-	-
Extrapersonal Neglect	-	+	+	+	-	-
Personal Neglect	-	+	+	+	-	-

Somatoparaphrenia	-	-	-	-	-	-

Table 1. Patients' demographic and clinical data

Presence (E+) or absence (E-) of embodiment of the experimenter's arm. Sex: M = Male, F = Female. General cognitive impairment: MOCA cut off ≥ 17/30 (Bosco et al., 2017). For visual field defect (the two values refer to the upper and lower visual quadrants, respectively), hemiplegia, hemianesthesia and anosognosia for hemiplegia scores were ranged from normal (0) to severe defects (3) (Pia, Spinazzola, et al., 2014; Pia et al., 2016; Piedimonte et al., 2015; Piedimonte, Garbarini, Pia, Mezzanato, & Berti, 2016; Spinazzola, Pia, Folegatti, Marchetti, & Berti, 2008); in HA we gave score equal to 1 to patients with tactile extinction; in AHP /= not assesable. Proprioception (- = no deficit; + = presence of deficit) assessed by means of the joint position matching task, whereby a patient is asked to recreate (i.e. match) a reference joint angle (i.e. position) in the absence of vision (i.e. using proprioceptive information) (Goble, 2010). 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 and coworker (Fotopoulou et al., 2011).

EXP 1	ALIEN CONDITION						OWN CONDITION					
	Ownership statement			Sensation statement			Ownership statement			Sensation statement		
	E+1	E+2	E+3	E+1	E+2	E+3	E+1	E+2	E+3	E+1	E+2	E+3
vs Controls	t= 4.25 *p= 0.001 Z-CC= 4.485	t= 5.05 *p= 0.0003 Z-CC= 5.697	t= 4.83 *p= 0.001 Z-CC= 5.091	t= 1.85 *p= 0.05 Z-CC= 1.958	t= 2.14 *p= 0.03 Z-CC= 2.257	t= 1.85 *p= 0.05 Z-CC= 1.958	t= -0.553 p= 0.29 Z-CC= -0.583	t= 0.10 p= 0.45 Z-CC= 0.112	t= -0.60 p= 0.28 Z-CC= -0.633	t= 0.43 p= 0.33 Z-CC= -0.462	t= 0.438 p= 0.33 Z-CC= -0.462	t= 0.438 p= 0.33 Z-CC= -0.462
vs E- patients	t= 26.812 *p= 0.001 Z-CC= 30.96	t= 33.74 *p= 0.0004 Z-CC= 38.96	t= 30.276 *p= 0.0005 Z-CC= 34.96	t= 68.416 *p= 0.0001 Z-CC= 79.00	t= 77.076 *p= 0.0001 Z-CC= 89.00	t= 68.416 *p= 0.0001 Z-CC= 79.00	t= -0.5 p= 0.33 Z-CC= -0.578	t= 0.37 p= 0.37 Z-CC= 0.43	t= -0.56 p= 0.31 Z-CC= -0.65	t= 0.372 p= 0.37 Z-CC= -0.430	t= 0.372 p= 0.37 Z-CC= -0.430	t= 0.372 p= 0.37 Z-CC= -0.430

Table 2. Experiment 1: Single subject analysis.

Significance test on difference between case's score and control sample, both healthy subjects and E- patients group. Z-CC: effect size for difference between case and controls (plus 95% CI), *p<0.05.

EXP 2	SYNCHRONOUS CONDITION						ASYNCHRONOUS CONDITION					
	Ownership statement			Sensation statement			Ownership statement			Sensation statement		
	E+1	E+2	E+3	E+1	E+2	E+3	E+1	E+2	E+3	E+1	E+2	E+3
vs Controls	t= 0.737 p= 0.241 Z-CC= 0.777	t= 0.951 p= 0.184 Z-CC= 1.002	t= 0.737 p= 0.241 Z-CC= 0.777	t= 1.176 p= 0.13 Z-CC= 1.234	t= 1.176 p= 0.13 Z-CC= 1.234	t= 0.639 p= 0.269 Z-CC= 0.670	t= 4.057 *p= 0.001 Z-CC= 4.255	t= 0.297 p= 0.387 Z-CC= -0.313	t= 4.564 *p= 0.001 Z-CC= 4.787	t= 5.155 *p= 0.0003 Z-CC= 5.406	t= 0.234 p= 0.41 Z-CC= -0.245	t= -0.381 p= 0.35 Z-CC= -0.4
vs E- patients	t= 0.716 p= 0.274 Z-CC= 0.827	t= 0.930 p= 0.225 Z-CC= 1.074	t= 0.716 p= 0.274 Z-CC= 0.827	t= 0.462 p= 0.344 Z-CC= 0.534	t= 0.462 p= 0.344 Z-CC= 0.534	t= -0.228 p= 0.420 Z-CC= -0.263	t= 20.457 *p= 0.001 Z-CC= 23.62	t= 1.732 p= 0.11 Z-CC= 2.00	t= -22.798 *p= 0.001 Z-CC= 26.32	t= 0.846 p= 0.243 Z-CC= 0.977	t= -0.398 p= 0.364 Z-CC= -0.46	t= -0.554 p= 0.317 Z-CC= -0.639

Table 3. Experiment 2: Single subject analysis.

Significance test on difference between case's score and control sample, both healthy subjects and E- patients group. Z-CC: effect size for difference between case and controls (plus 95% CI), *p<0.05.

Patients	Etiology	Lesion Side	Involved brain structures
***E+1**	H	RH	Basal ganglia, sub-cortical fronto-parietal periventricular white matter and middle temporal gyrus
E+2	I	RH	Basal ganglia (including caudate nucleus, putamen and globus pallidus) and sub-cortical fronto-parietal periventricular white matter (including uncinate fasciculus; internal capsule; external capsule, superior fronto-occipital fasciculus; superior longitudinal fasciculus; superior corona radiata)
***E+3**	I	RH	Thalamus and sub-cortical fronto-parietal periventricular white matter
***E-1**	I	RH	Superior temporal gyrus; insula; putamen; supramarginal gyrus; periventricular temporo-parietal white matter
E-2	I	RH	Superior temporal gyrus, supramarginal gyrus, rolandic operculum, insula, internal and external capsule and temporo-parietal periventricular white matter.
E-3	I	RH	Inferior and middle temporal gyrus, temporo-parietal periventricular white matter

Table 4. Patients' involved brain structures.

Etiology: H = hemorrhage; I = ischemia. Lesion Side: RH = Right Hemisphere; LH = Left Hemisphere. 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 & Brett, 2000). * For these patients, MRI or CT were not available and we reported the brain lesions according to the medical report.

FIGURE

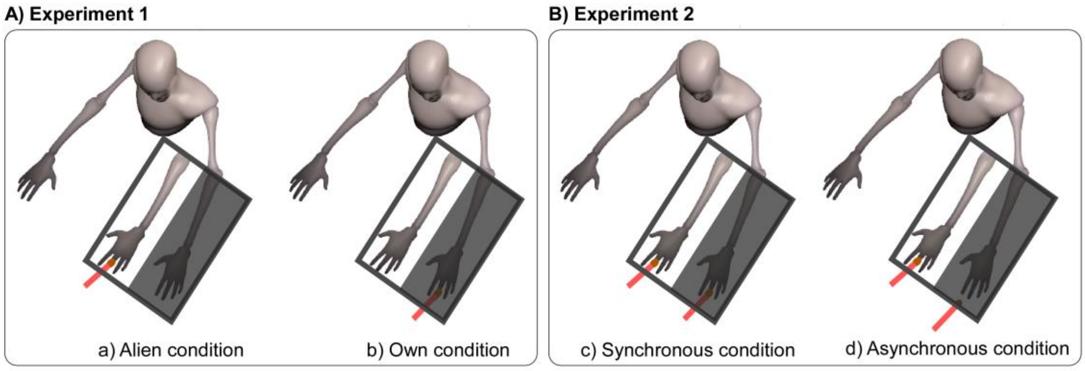

Figure 1. Experimental Conditions. Graphic representation of the experimental conditions in Experiment 1 (panel A) and in Experiment 2 (panel B).

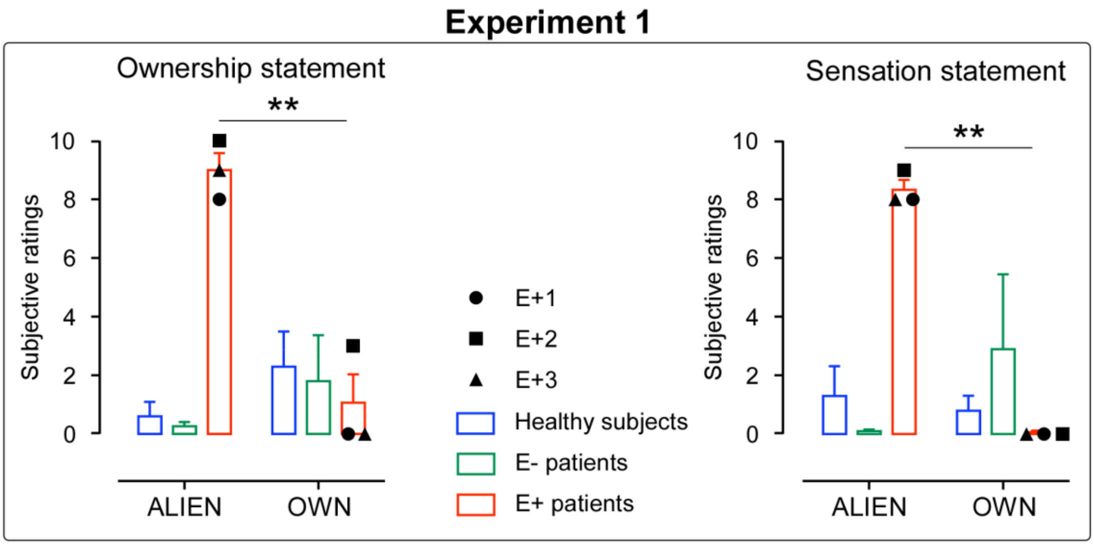

Figure 2. Experiment 1 results. Graphs show the mean subjective ratings with standard errors in the Own condition and the Alien condition, for both Ownership (left panel) and Sensation statement (right panel), in E+ patients (red), E- patients (green) and Healthy subjects (blue). Single subject's ratings are represented by means of different black icons (E+1: circle; E+2: square; E+3: triangle). ** $p < 0.005$.

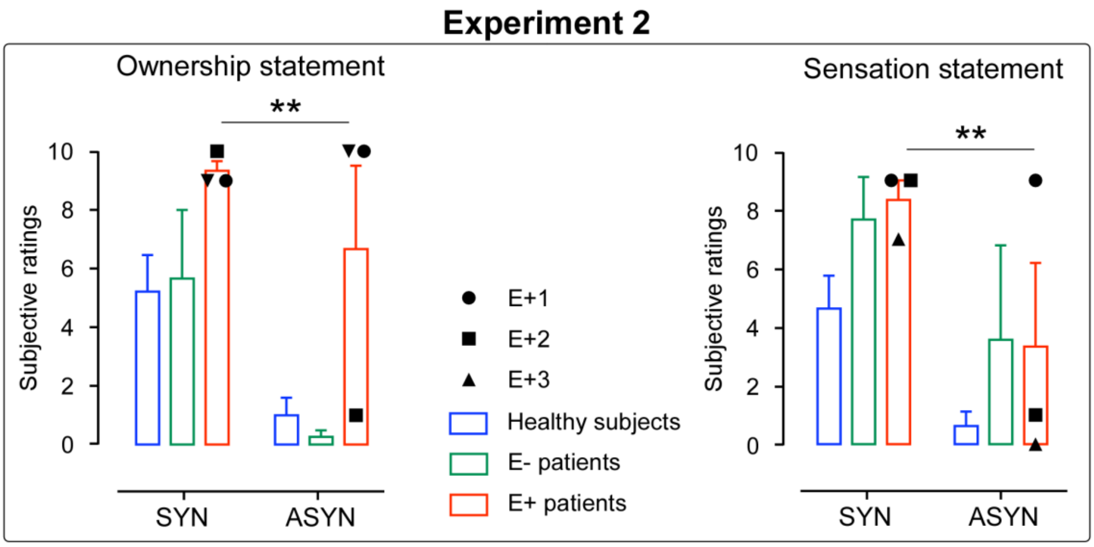

Figure 3. Experiment 2 results. Graphs show the mean subjective ratings with standard errors in the Synchronous and the Asynchronous condition, for both Ownership (left panel) and Sensation statement (right panel), in E+ patients (red), E- patients (green) and Healthy subjects (blue). Single subject's ratings are represented by means of different black icons (E+1: circle; E+2: square; E+3: triangle). ** $p < 0.005$.

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