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The 'healthy side' of anosognosia for hemiplegia: Increased sense of agency for the unimpaired limb or motor compensation?

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ABSTRACT

Objectives: Anosognosic patients show a lack of awareness for their hemiplegia coupled with a distorted sense of agency for the actions performed by the plegic limbs. Since anosognosia is often associated with right brain damage, this hemisphere seems to play a dominant role in monitoring awareness for motor actions. Therefore, we would expect that anosognosic patients show distorted awareness and sense of agency also for actions performed with the unimpaired limb.
Method: To test this hypothesis, we induced illusory actions that could be congruent or incongruent with a preceding verbal command. A group of 16 right brain-damaged patients performed this task and then rated i) their ability to anticipate the actions, ii) their sense of agency and iii) their sense of ownership for each limb. Measures of awareness, neglect and motor impairment were also considered for the patient group.
Results: Following incongruent actions with the unimpaired limb, less aware patients showed a relatively mild distortion in all three aspects. In addition, we also found a crucial relationship between motor impairment (for the plegic limb) and sense of agency for both plegic and healthy limbs.
Conclusion: Although the distortion linked to both limbs supports the initial hypothesis that the right hemisphere is responsible for monitoring awareness for action for the whole body, our data also suggest that the observed distortion may be linked to a motor compensatory phenomenon, not necessarily related to awareness processes.

1. Introduction

Patients with motor impairment following brain damage may show a lack or reduction in awareness for their impairments (anosognosia for hemiplegia; Mograbi and Morris, 2018). "Anosognosia is inferred from the discrepancy between patient self-report and/or actions with informant report or an objective evaluation, such as a neurological examination/neuropsychological test" (Mograbi and Morris, 2018, p. 385). Despite the fact that this syndrome has also been observed following left brain damage (e.g. Cocchini et al., 2009), anosognosia is generally more frequent and severe following lesions in the right hemisphere (Mograbi and Morris, 2018). The degree, extent and specificity of unawareness can vary considerably with patients firmly denying their hemiplegia while others tend to only underestimate their motor problems (Marcel et al., 2004; Prigatano, 2010) or the motor task difficulty (e.g. Cocchini et al., 2018).

Anosognosic patients may also show a distorted sense of agency. Sense of agency refers to the feeling of controlling actions and their effects (Moore, 2016; Haggard, 2017); these patients will typically experience a sense of agency in the absence of movement (e.g., Karnath and Baier, 2010; Moro et al., 2021). The aberrant presence of agentic experience is intriguing given that it contradicts the compelling sensory evidence pointing towards the patient's motor impairment. Not surprisingly, several theories have been offered to explain possible dissociations in anosognosia for hemiplegia and related underlying mechanisms. An interesting approach relies on the Comparator Model, a useful model that has been adopted to explain sense of agency for actions and anosognosia. This model describes the cognitive steps required

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to compare motor intentions with the observed output (Wolpert et al., 1995; Frith et al., 2000). According to this model, the motor efferent copy, generated by an individual's intention to move, would result in a specific prediction of the outcome. A comparator would then detect possible discrepancies between expectation and sensory feedback. The outcome of this comparison informs agency attributions. In the context of anosognosia for hemiplegia, Blakemore et al. 2002 suggested that the malfunctioning of different components of this motor model can affect the outcome of the comparator, resulting in an incorrect belief of self-generated actions and a distorted sense of agency over movements that have not been executed (see also Mograbi and Morris, 2013 for a detailed analysis). Adopting the rubber hand paradigm, Fotopoulou et al. (2008) experimentally investigated whether there is a dominance of motor planning over the sensory feedback in four hemiplegic patients inducing illusory 'movements' of their motionless limb. Anosognosic patients tended to report movements of their 'fake' hand incorrectly when they were first instructed to move ('self-generated' condition). Interestingly, these patients were able to acknowledge the absence of movement when the instruction required them to detect movements of their [fake] hand moved by the examiner ('externally-generated' condition). Their accuracy in reporting the absence of passive externally-generated movements suggests that feedback information was processed accurately. This also suggests that, when asked to self-generate a movement, anosognosic patients' intention to move their own paretic limb dominates and 'overwrites' the actual sensory feedback generating a false sense of agency for actions that never occurred.

The inability to detect discrepancies between motor predictions and sensorimotor feedback can explain on-line monitoring deficits during actions but is insufficient to explain the complex pattern of anosognosia symptoms (e.g., Marcel et al., 2004). It also does not account for evidence of implicit awareness during execution of motor tasks (Cocchini et al., 2010; Moro et al., 2011). Therefore, anosognosia may be determined by a series of factors that could affect the process of becoming aware (e.g., Levine et al., 1991; Marcel et al., 2004; Davies et al., 2005; Vuilleumier, 2004; Heilman, 2014; Fotopoulou, 2014). Neuroanatomical results (Pacella et al., 2019) support this general hypothesis showing that awareness for own limb impairment is associated with a wide right hemisphere network that encompasses the premotor system (pre-SMA, striatum and inferior frontal gyrus, involved in action monitoring, Berti et al., 2005, 2007; Vocat et al., 2010, Moro et al., 2016), the ventral attentional system (i.e., via superior longitudinal fasciculus III connecting the temporo-parietal junction and the ventral frontal cortex; responsive to the salient stimuli regarding one's own paralysis, Vocat et al., 2010; Gandola M. et al., 2014) and the limbic system (i.e., disconnections via the cingulum of the limbic system structures and the insula that have an important role in the sense of self and beliefs updating during the processing of errors, Karnath et al., 2005; Baier and Karnath, 2008; Vocat et al., 2010; Fotopoulou, 2014; Moro et al., 2016).

In this context, while anosognosia represents a measure of lack of awareness for motor impairment, sense of agency represents the productive aspect of anosognosia as it indicates and experience of control over a movement that never occurred. In particular, in line with Berti et al.'s (2005; see also Berti et al., 2007) findings, Heilman (2014; see also Heilman, 1991) suggested that a premotor-basal ganglia network would be responsible for generation of motor intention and efferent copies, whereas the right insula, a crucial area for integration of multimodal sensory information, could represent the anatomical substrate of the comparator. The degree of sense of agency is closely linked to the activation of the right insula and the right pre-frontal areas (Farrer et al., 2003; Karnath et al., 2005), which are also crucial areas for anosognosia. These findings suggest a partial overlapping of awareness and sense of agency networks, which assures a realistic sense of agency for own actions and, if lesioned, underlies anosognosia. However, recent studies have expressed some doubts about the exclusive role of the right hemisphere network over both awareness and agency. On the one hand, anosognosia following left brain damaged seems to be more frequent than expected (e.g., Hartman-Maeir et al., 2003; Cocchini et al., 2018) and its evidence may have been historically underestimated because of methodological issues (Cocchini et al., 2009). On the other hand, recent neuroimaging studies on healthy participants (e.g., Seghezzi et al., 2019; Di Plinio et al., 2020; Zapparoli et al., 2020; see also Zito et al., 2020 for a meta-analysis) have identified broader bilateral networks related to the sense of agency. By means of fMRI and rTMS studies, Zapparoli et al. (2020) observed the crucial role of the pre-supplementary motor area during intentional binding when action was planned. In particular, Seghezzi et al. (2019) found support of an integrated model of agency and body-ownership with a shared network in the left middle insula and a specific-agency network involving both left (i.e., supramarginal gyrus and posterior insula) and right (i.e., postcentral gyrus and superior temporal lobe) areas. These latest observations lead to very different predictions of the hemispheric role on both awareness and motor monitoring, suggesting a not exclusive role of the right hemisphere. It follows that networks relying on the two hemispheres may cover different cognitive steps of these aspects or that they may play a crucial role for each contralateral body side.

In line with the aforementioned hypothesis of the dominant right-hemisphere network role on awareness and agency, we would expect to observe that distortion of both components would not be limited to the contralesional side as this network would be responsible for monitoring actions performed with any part of the body. In other words, we would expect that anosognosic patients show distorted sense of agency for actions performed with both contralesional and ipsilesional limbs. However, since ipsilateral motor ability is typically spared, the crucial discrepancy between intention and sensory feedback is not replicable for the 'healthy side' and the potential distortion of sense of agency and awareness may remain 'hidden'.

In light of this, a few key research questions seem to emerge. Firstly, if the right-hemisphere network is responsible for ensuring a realistic monitoring of actions, correct awareness of possible impairment and realistic sense of agency, we would expect that the same network is also responsible for ensuring similar processes for actions performed with both limbs. This would also explain why anosognosia is more frequent after lesions of the right hemisphere. In a similar way, if anosognosic patients suffer from a general deficit in updating self-referred beliefs regarding their body and their capacity to do actions, they should show updating deficits in actions performed by both limbs. On the other hand, in support of the bilateral networks for agency and awareness, if anosognosia for hemiplegia is a specific distortion of awareness and sense of agency only for the left limb, then we have to assume that a different network may be responsible for motor monitoring of the right limb and we should find deficits confined to the contralesional limb in anosognosia.

Two previous studies have investigated this research question considering the accuracy of patients' recall for motor information. Preston et al. (2010) investigated awareness for reaching movements performed by the healthy limb in a right-brain damaged anosognosic patient. Visual feedback was manipulated to induce differing degrees of mismatch between action and feedback. The patient showed some difficulties in detecting visual incongruences. Similarly, in a more recent study by Saj et al. (2014), five anosognosic patients were asked to either imagine or perform a series of actions with their contralesional (impaired) and ipsilesional (unaffected) limb. Patients were then asked to recall whether each action was previously 'acted' or 'imagined'. Anosognosic patients showed a difficulty in remembering the source of 'actions' even when it involved the healthy limb. However, because of the nature of hemiplegia, in both studies a direct comparison between limbs was not possible as the impaired limb was not tested in the same condition. Moreover, patients' responses were limited to detection of incongruence between action and feedback. Capitalising on these two previous studies, we aimed to further investigate agency and ownership for action and limbs during a vicarious agency paradigm. In particular, we will be interested in assessing to what degree hemiplegic patients

Table 1
Patients' demographical and clinical information.

Gender	Age (yrs)	Education (yrs)	Lesion site	Onset from lesion (mths)	Motricity Index (1–100)
11 Males 5 Females	M = 62.56 SD = 13.06 Range:41-85	M = 8.69 SD = 3.63; Range:5-17	Right	M = 3.54 SD = 3.22 Range:0.8–12.2	M = 13.06 SD = 14.52 Range:1-48

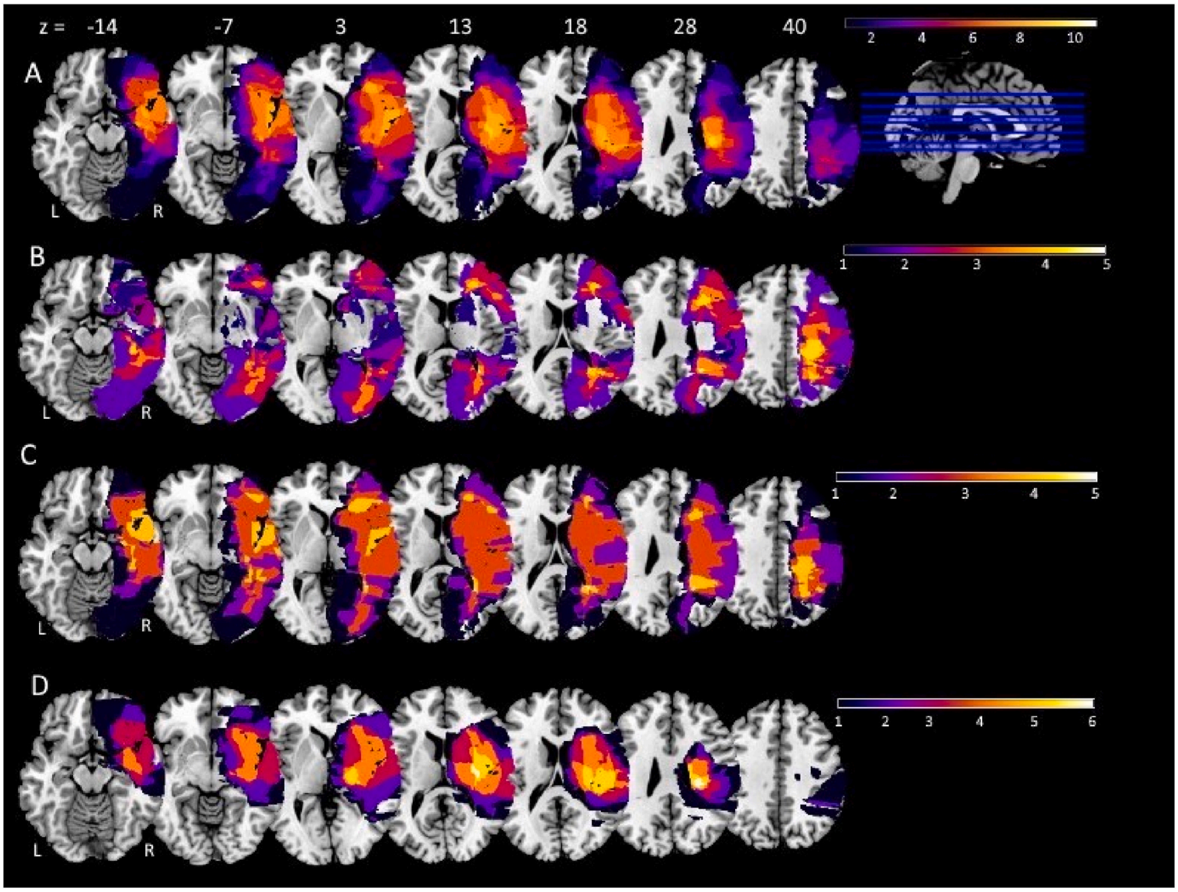

Fig. 1. Overlapping of patients' lesions. The lesions of 11 right hemisphere damaged patients were drawn and superimposed in a ch2. nii.gz template (MRIcron) and analysed based on the AAL template (Automated Anatomical Labeling, Tzourio-Mazover et al., 2002). A) Overlapping of patient's lesions (AHP + HP = n. 11 patients); B) Differences between AHP and HP patients shown by the subtraction procedure (AHP-HP = n.5); C) Overlapping of AHP patients' lesions (AHP = n.5); D) Overlapping of HP patients' lesions (HP = 6 patients). The areas associated with AHP involve the ventral and medial frontal areas, insula, dorsal parietal and occipital areas. Due to the small numbers of patients in the two groups, no further statistical analyses were performed.

tend to experience incongruous information for illusory motor actions 'performed' by each limb.

A second caveat concerns the nature of the abnormal sense of agency in anosognosia. Several studies have argued that both anosognosia and agency are multifactorial and different sources of information contribute to sense of agency (e.g., Nurmi and Jehkonen, 2014 for a revision of anosognosia; Synofzik et al., 2008; Moore and Fletcher, 2012 for sense of agency). One of these factors is linked to an abnormally strong intention to move guided by prior expectations about movements (Fotopoulou et al., 2008); following this hypothesis we would expect to observe an exaggerated feeling of agency and anticipation of an action's outcome in all conditions regardless of whether the sensory feedback is congruent or incongruent with the intended action. On the other hand, if anosognosia is mainly linked to a general monitoring impairment (e.g., Saj et al., 2014), we would expect to only observe a distorted feeling of agency and anticipation when the feedback information is incongruent with the action, whereas patients showing anosognosia would perform similarly to hemiplegic patients and healthy controls when action and feedback are congruent.

Finally, although anosognosia for hemiplegia and asomatognosia (i. e. the unilateral disturbance of ownership) represent two different clinical conditions (Jenkinson et al., 2018), a close relationship lies between sense of agency and sensation of limb ownership (e.g., Baier and Karnath, 2008). In some studies, anosognosic patients showed agency in the movements performed by a rubber hand (Fotopoulou et al., 2008), which implies a prior embodiment of the fake hand. Thus, it would be interesting to explore whether anosognosia reflects a particular embodiment tendency and whether possible distortions affect both limbs similarly.

It becomes, therefore, crucial to find a paradigm that recreates a direct intention-sensory discrepancy for the ipsilesional (unimpaired) limb and measures motor intention/anticipation, sense of agency and ownership for differing degrees of congruency between internal motor instruction and outcome (Moore, 2016). Paradigms adopting illusion of movements can offer a unique opportunity to mimic such a discrepancy and investigate all these aspects, also for the healthy limb. To this aim, we capitalised on previous studies (Wegner et al., 2004; Cioffi et al., 2017) with healthy volunteers to evaluate motor anticipation, sense of agency and sense of ownership in anosognosic patients with right brain lesion by inducing illusory movements of impaired and unimpaired limbs. Despite both limbs being evaluated in our study, our main interest is to investigate the sense of agency and ownership for the healthy limb. In detail, if the right-hemisphere network plays a dominant role on motor awareness, we would expect to observe a distorted sense of agency and ownership also for the unimpaired ipsilesional limb. Firstly, we would expect that the degree of distortion is greater for more severe cases of anosognosia with no specific relationship with the severity of the motor impairment. Secondly, since anosognosia has been linked to a strong motor intention that can override sensory feedback about the action (Fotopoulou et al., 2008), we would expect a greater distortion when patients need to take into account action feedback that is incongruent with the motor intention. In this case, anosognosic patients would provide significantly higher ratings than aware controls in this specific condition.

To summarize, the current study's main aim is to investigate the impact of right hemisphere damage on sense of agency for vicarious movements of the healthy limb and its relationship with anosognosia.

2. Materials and method

2.1. Partici[1]pants

An initial group of 19 (13 males) brain damaged patients was recruited at the IRCSS Sacro Cuore Don Calabria Hospital in Verona (Italy) and the service de Médecine Physique et Réadaptation Neurologique of the Centre Hospitalier in Saint-Amand-Les-Eaux (France). Clinicians, informed of the topic of the study, were asked to refer patients with a brain lesion who were showing motor impairment. Patients showing relevant comprehension language disorders at an informal interview were not included as aphasia could affect their understanding of the Vicarious Motor Task (described below). The degree of motor impairment for upper limbs was then formally assessed by means of the Motricity Index (Wade, 1992) where a score of 1 indicates 'no movement' and a score of 100 indicates normal motor power. To enter the study, patients had to present an evident motor impairment in their contralesional upper limb and obtain a score below 50 on the Motricity Index which indicates a clear lack of range of movement for the upper limb. Three patients showed too mild of a motor impairment, obtaining a score of 63, 71 and 72 on the Motricity Index so they were excluded. A final group of 16 patients (11 males), all right-handed (Edinburgh Handedness scale, Oldfield, 1971), showed a moderate/severe motor impairment and scored below the cut-off of 50 on the Motricity Index (see Table 1). None of the patients showed evidence of apraxia on clinical examination.

In this initial phase either the clinician or the examiner clinically evaluated patients' awareness for the upper limb impairment by means of the Anosognosia Scale (Bisiach et al., 1986a) that evaluates patients' responses to some questions about their motor impairment on a 4-point scale. Patients who verbally report their motor deficit either spontaneously (score = 0) or after a question about the strength of their limb (score = 1) are deemed as aware; those who do not acknowledge their motor impairment following a specific question about the strength of their limbs (score = 2) or after a demonstration of the motor impairment (score = 3) are deemed as anosognosic (Baier and Karnath, 2008). A score of 1.5 is assigned if the patient acknowledges a general motor impairment not related to hemiplegia but to other causes (e.g. previous surgical operation or arthrosis) (D'Imperio et al., 2017). One patient showed clear evidence of anosognosia (score = 3), two patients obtained a score of 1.5 and all other patients obtained a score of 0 (9 patients) or 1 (4 patients).

Table 1 shows the demographic and clinical information of the final group. All 16 patients had a unilateral lesion on the right hemisphere. Fig. 1 illustrates the lesion reconstruction of 11 patients.

The study was approved by the local research committee of each site and conducted in accordance with the Helsinki Declaration. All participants gave informed consent prior to taking part in the study.

2.2. Method and procedure

2.2.1. General cognitive assessment

Patients were asked to complete the Mini Mental State Examination (MMSE; Folstein et al., 1975).

Personal neglect was assessed by means of the Comb and Razor/Make-up test (Beschin and Robertson, 1997; McIntoch et al., 2000) or the One Item test (Bisiach et al., 1986b). Extrapersonal neglect was assessed by means of a battery of tests, which included Line Cancellation (Albert, 1973), Line bisection (Wilson et al., 1987) and Clock test (Mondini et al., 2011). Pathological performance on at least one of these tests was considered as evidence of extrapersonal neglect.

2.2.2. Awareness for motor impairment

Due to the variability of anosognosia symptoms (e.g., Marcel et al., 2004) and recent considerations about a limited use of assessment tools in anosognosia studies (Nurmi and Jehkonen, 2014), in addition to the Anosognosia scale (Bisiach et al., 1986a; Berti et al., 2005), another test (i.e. Visual Analogue Scale for motor impairment; VATAm; Della Sala et al., 2009) was used in order to assess patients' awareness for motor impairment. The VATAm consists of two sub-scales to separately assess awareness for upper (8 questions on bimanual tasks) and lower (4 questions on bipedal tasks) limbs' impairment. Due to the main experimental task (Vicarious Motor Task, described below), we were particularly interested in the degree of awareness for the upper limb impairment, so we considered ratings on the upper limb sub-scale. Patients' scores were then compared with ratings provided by an informant. The upper limb discrepancy (patient rating *minus* informant's rating) can range from −24 to +24. A discrepancy of zero indicates a perfect agreement between patient and informant, whereas positive and negative discrepancy values indicate patients' overestimation or underestimation of their own motor abilities respectively (Della Sala et al., 2009).

In order to distinguish between anosognosic (AHP) and aware (HP) patients, these were clusterised using their scores on both the VATAm (Della Sala et al., 2009) and the Anosognosia Scale (Bisiach et al., 1986a). The number of clusters was computed by means of the Silhouette method (Rousseeuw, 1987), and the clusters were aggregated by means of the kmeans algorithm (Hartigan and Wong, 1979).

These statistical analyses were computed using R ver. 4.0.0 (R Core Team, 2020) and the R package factoextra ver 1.0.7 (Kassambara and Mundt, 2020).

2.2.3. Vicarious motor task

This task measures motor anticipation, sense of agency and sense of ownership. Following Cioffi et al.' s (2017; Wegner et al., 2004) procedure, participants were asked to sit in a chair facing a full-length mirror at about 1 m away and listened to a list of instructions to perform specific gestures (e.g., "wave") through headphones. Participants' arms remained still on their laps, out of view under the sheet that covered all participants' body from the shoulders down. The examiner stood behind the participants' chair, hidden by a shield that was placed behind the participants' back (see Fig. 2).

The examiner wore another set of headphones to hear the instructions, a blouse with the same sheet-colour and a pair of cotton gloves. She placed her arms forward so that they appeared where the participant's own arms would have been. Participants were asked to remain still and not move their arms for the entire duration of the experiment and to look at the mirror while the examiner performed the

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[1] For the purpose of meta-analyses, 10 patients also entered other studies (Pacella et al., 2019; Moro et al., 2021).

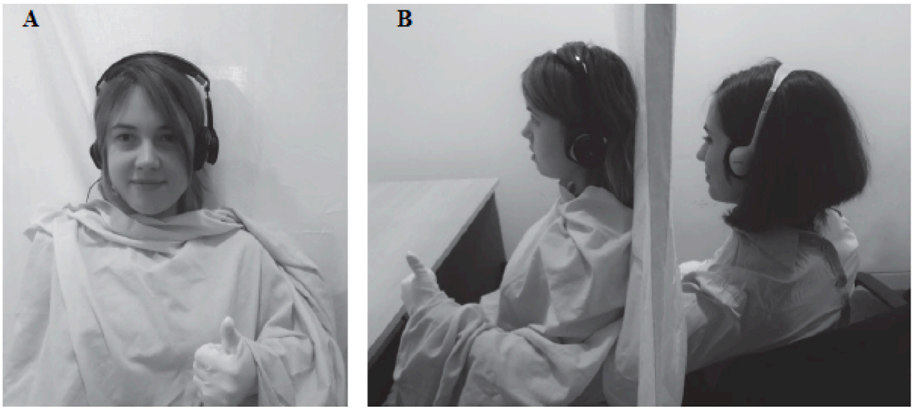

Fig. 2. Experimental set-up (based on Cioffi et al., 2017). Panel *A* shows what the participants could see in the mirror placed in front of them. Panel B shows the set-up from the side, with the examiner sitting behind the participant and putting her hand forward so that it appears where the participant's hand would normally be (Reproduced from Cioffi et al., 2017 with authors' permission).

gestures with either the left or the right hand (the order was counterbalanced within participants). Breaks between conditions were allowed. Importantly, participants were informed in advance whether they had to pay attention to the left or right limb. With clinical population, a second examiner sat behind the mirror for the entire duration of the experiment to remind patients, at the beginning of each block, which side to move their attention and to ensure they comply.

A tape with a list of 16 action instructions was played (e.g., "snap the fingers", "point to the mirror"; see Supplementary Table for the full list of actions). Instructions were recorded at about a rate of 8–10 s with a few seconds between the end of an action and the next instruction. The examiner started each action immediately after the end of the relative instruction.

There were two conditions where the same list of 16 actions was presented three consecutive times. In the *match condition* the gesture corresponded to the instruction; whereas in the *mismatch condition* each instruction was matched with a random non-related gesture (e.g. after the instruction "wave" the examiner snapped her fingers). In this last condition, the non-related gesture was different for every repetition of the same instruction (e.g., on the second trial, after the instruction "wave" the examiner pointed to the mirror). The order of match – mismatch conditions was counterbalanced across participants.

An initial practice phase consisted of 3 match and 3 mismatch trials to ensure understanding and to allow participants to familiarise themselves with the task. The practice trials were repeated until the participant was confident to start and they showed an understanding of the task instructions. The instructions/gestures used for practice purposes were not included in the main experimental phase.

As in Cioffi et al. (2017), the whole list of 16 instructions was repeated from the beginning to the end without interruption 3 times for each condition and each hand (4 blocks). Each block lasted approximately 8–10 min. At the end of each block (e.g. left hand-match condition), the participants were asked to answer 3 questions using a 7-point scale from 1 (not at all) to 7 (very much).

The questions were the same as the ones included in previous studies using this paradigm (Wegner et al., 2004; Cioffi et al., 2017):

- *Check question*- Anticipation: "To what degree did you feel you could anticipate the movements of the arm?" to check that participants were attending to the prime-action relationship. High ratings in the match condition suggest that the participant could anticipate what type of action was to be performed after hearing the verbal instruction.
- *Sense of Agency*: "How much control did you feel that you had over the arm's movements?"
- *Sense of Ownership*: "To what degree did the arm feel like it belonged to you?''

2.2.4. Statistical analyses

Taking into consideration the necessity of a statistical modelling approach that is able to manage the ordinal nature of the dependent variables, the small sample, and the need to capture both alternative and null hypothesis results, data were analysed by means of a Bayesian approach (de Laplace, 1825; Gelman et al., 2013). The Bayesian approach uses prior distributions that represents the hypothesis of the study. In this study we adopted conservative priors, where regressors are normally distributed with mean 0 and standard deviation 1. The results are given in terms of posterior distributions, which are the distributions obtained by the multiplication of the likelihood distribution of the data and the prior distributions, extracted by means of Hamiltonian Markov Chain sampling (HMC, Carpenter et al., 2017) with 4 chains with 1000 burn-in iterations and 1000 iterations for the statistical computation, for a total of 4000 iterations. Results from the posterior distributions are summarised in terms of 95% Credible Intervals (95%CI) and Bayes Factors (BF_{10}), computed by means of the Savage-Dickey method (Wagenmakers et al., 2010). Traditionally, with a $BF_{10} > 3$ the alternative hypothesis is considered valid (i.e., the presence of a difference), while the null hypothesis (i.e., the absence of a difference) is considered valid when there is a $BF_{10} < 1/3$ (Raftery, 1995). BF_{10} between 3 and 1/3 are considered inconclusive (i.e., the evidence is neither in favour of the presence nor the absence of a difference).

In order to check the quality of the Bayesian models, the Bulk and Tail Effective Sample Size (Gelman et al., 2013), the Posterior Predictive plots (Gelman et al., 2013) and the Gelman and Rubin's diagnostic (Gelman and Rubin, 1992) were computed. The former is the total number of stationary HMC iterations corrected by the autocorrelation among four HMCs (good values are greater than or equal to 10% of total samples, namely 400), the Posterior Predictive plots show the overlapping of real data with the data predicted by the model, and the latter shows if the chains of the HMC are converging towards the same range of values ($\hat{R} = 1$) or diverging ($\hat{R} > 1.1$). In all cases, these checks showed that the models are reliable, and are available in the Supplementary Material.

In the main text, Bayesian results are shown in terms of mean (in the text reported as "β") and 95% Credible Interval of the Posterior Distribution, and BF_{10}. Here only the results suggesting the acceptance of the null or alternative hypothesis are reported. For the whole representation of data, please see the Supplementary Material.

All subjective answers were analysed by means of Bayesian Ordinal models. Ordinal models can use a different link function, depending on the characteristics of the dependent variable. The link function can be a

Table 2

Individual performance on motor and cognitive tests.

Patient N/Cluster	Motricity Index	MMSE	Bisiach scale	VATAm	PN			EN
						One item test	Comb & Razor/Makeup test	(Lines C., Bisection; Clock)
1/HP	**15**	/	0	0	PN-	0	−0.028	N+ (++/)
2/HP	**1**	24.45	1	2	PN-	0	/	N- (—)
3/HP	**10**	27.9	0	1	PN+	0	**−0.485**	N+ (+-+)
4/HP	**30**	26.99	0	3	PN+	0	**−0.145**	N+ (–+)
5/HP	**1**	**21**	1.5	1	PN+	**1**	0	N- (–/)
6/HP	**24**	**22.9**	0	5	PN+	**1**	**−0.44**	N+ (+++)
7/HP	**1**	**23.49**	0	5	PN+	0	**−0.475**	N- (//-)
8/HP	**1**	28	0	6	PN+	0	**−0.375**	N+ (+++)
9/HP	**25**	/	0	8	PN-	0	−0.045	N+ (-+/)
10/AHP	**1**	30	1	11	PN+	**1**	**−0.3**	N- (//-)
11/AHP	**1**	**16.3**	1	14	PN+	**1**	**−0.125**	N+ (+++)
12/AHP	**1**	**18.89**	3	14	PN+[a]	0	**0.28** [a]	N+ (/++)
13/AHP	**19**	26.2	1.5	18	PN-	0	−0.055	N+ (–+)
14/AHP	**24**	**23.62**	0	12	PN+	0	**−0.29**	N+ (-++)
15/AHP	**1**	**21.4**	0	15	PN+	0	**−0.605**	N+ (-++)
16/AHP	**21**	27.3	1	11	PN-	0	0.08	N+ (–+)

Pathological performance on Motricity, MMSE and PN (based on normative data) in shown in bold.
+ indicates evidence of EN; - indicates no evidence of EN;/indicates test not performed.
[a] Ipsilesional neglect.

probit or a logit function, with symmetric, equidistant or flexible boundaries among ordinal scores. For this reason, before starting with statistical analysis, we determined the nature of the link function by using the Akaike Information Criteria. In all cases the best function was the logit one with flexible boundaries (see Supplementary Material).

The Anticipation, Ownership and Agency scores were analysed separately, using as independent variables the Cluster of patients (obtained by the k-means application; i.e. anosognosic/aware patients), the Limb (Healthy/Hemiplegic), the Condition (Match/Mismatch) and all the interactions.

These analyses had the purpose of investigating the specific hypothesis that awareness can impact Sense of Agency and Sense of Ownership during vicarious motor tasks. However, putative differences between AHP and HP patients might be better explained by personal neglect or motor impairment. For this reason, the dependent variables, whose analyses showed credible effect of the Cluster, were also analysed by means of the Bayesian Ordinal Covariation model, with the independent variables that reached BF10 > 3 and, as continuous covariates, the score in the Motor Index and Personal Neglect tests. In order to avoid any statistical biases, the Motor Index and Personal Neglect scores were transformed into z-scores, using the mean and standard deviation of the current sample, in order to have two continuous variables with a similar range and mean zero.

3. Res[2]ults

3.1. General cognitive assessment

Fourteen patients out of 16 completed the MMSE. Individual MMSE scores were corrected by age. On average patients obtained a score of 24.17 (SD = 3.87; range = 16.3–30) with 7 patients performing below normal range (See Table 2). An independent *t*-test showed no significant difference between the groups (t-crit = 0.749; p = .469).

All 16 patients completed the One Item test and 4 of them showed evidence of mild personal neglect. Fifteen patients completed the Comb and Razor/Make up test and 10 (66.7%) of them showed either contralesional (9 patients) or ipsilesional (1 patient) personal neglect. The patient who did not carry out the Comb and Razor/Make up test, completed the One Item test and his performance was flawless. All 16 patients completed at least 1 extrapersonal neglect test, with 10 patients completing all three tests and 4 patients completing two tests. Overall, 4 patients showed normal performance on all tests, whereas the other 12 (75%) patients showed evidence of contralesional extrapersonal neglect. No patient showed evidence of ipsilesional extrapersonal neglect (See Table 2).

3.2. Awareness of motor impairment

All patients completed the VATAm and they provided correct responses to the check questions. Therefore, they were all considered for the final analyses.

The Silhouette plot on the raw scores of the Anosognosia Scale and on the VATAm suggested to use clusters (see Fig. 3).

Therefore, the kmeans algorithm was used to find two clusters, grouping the patients between aware – mild anosognosia (HP group, 9 patients) and moderate – severe anosognosia (AHP group, 7 patients) (see Table 2).

Motricity Index data across groups were analysed by means of a non-parametric test as normal distribution for the AHP group cannot be assumed (Shapiro-Wilk test p = .001). HP and AHP groups did not show a significant difference in the degree of motor impairment assessed by means of the Motricity Index (AHP mean = 9.71; SD = 10.34, median = 1, range = 1–24; HP mean = 15.67; SD = 16.21; median = 10, range = 1–48; Mann-Whitney U = 632, z = 1.855, p = .07; r = −0.23). A Spearman correlation did not show a significant relationship (*rho* = −0.202; p = .436) between degree of unawareness (VATAm scores) and motor impairment (Motricity index scores).

Finally, 6 out of 9 (67%) HP and 4 out of 7 (57%) AHP showed contralesional personal neglect (note that 1 AHP showed ipsilesional personal neglect). Considering the extrapersonal component, 6 out of 9 (67%) HP and 6 out of 7 (86%) AHP showed extrapersonal neglect. Degree of unawareness (i.e. VATAm scores) was correlated with the patients' performance on each of the personal and extrapersonal neglect tests. No significant correlation was found between unawareness and personal neglect (lowest p = .705), nor with the other three tests assessing extrapersonal neglect (lowest p = .07).

3.3. Vicarious motor task

3.3.1. Anticipation question

The Bayesian Ordinal Model (see Fig. 4) showed that the null

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[2] **Data and materials availability**. The data and the scripts for the analyses are available online (https://osf.io/5pny9/. Click or tap if you trust this link.">https://osf.io/5pny9/).

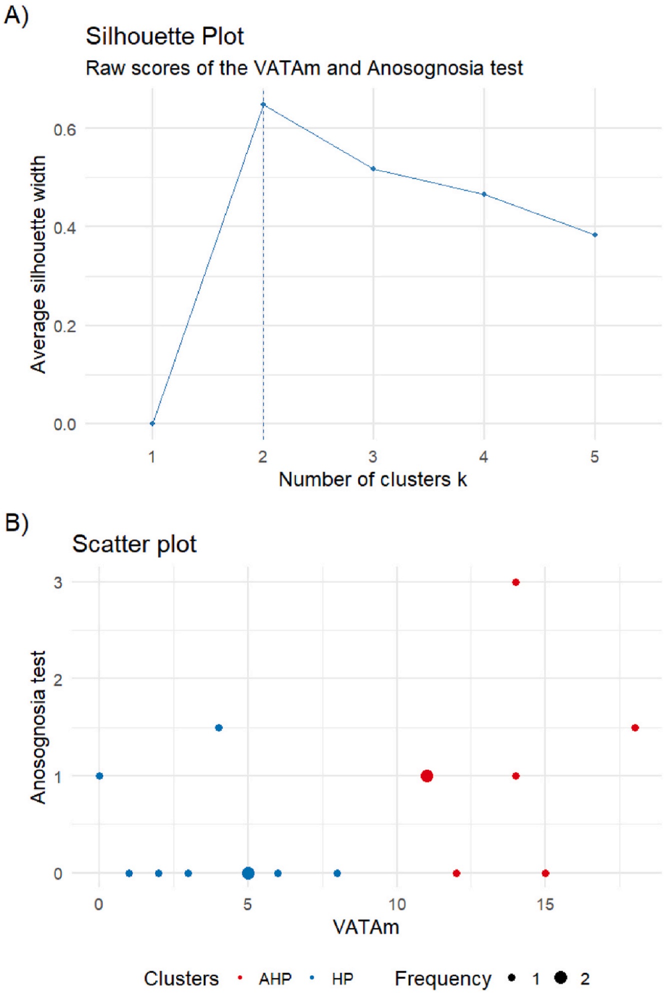

Fig. 3. Silhouette plot and clusterisation of patients. Panel *A* shows the Silhouette plot on the VATAm and Anosognosia test raw scores, suggesting two clusters. *Panel B* shows the clusterisation of participants into AHP and HP groups, according to their VATAm and Anosognosia test scores. The size of the points represent the number of patients with that specific combination of VATAm and Anosognosia test scores These analyses were repeated on the z-scores of the two tests for robustness, confirming the results, and are available on the Supplementary Materials.

hypothesis is confirmed for the Limb factor ($\beta = 0.04$, 95%CI = −0.39, 0.47, $BF_{10} = 0.2$) and for the interactions between Cluster and Condition ($\beta = 0.18$, 95%CI = −0.24, 0.63, $BF_{10} = 0.3$) and between Cluster, Limb and Condition ($\beta = 0.13$, 95%CI = −0.29, 0.55, $BF_{10} = 0.3$).

The Condition effect showed the presence of a difference ($\beta = 0.61$, 95%CI = 0.17, 1.07, $BF_{10} = 5.5$) between the Match ($\beta = 4.57$, 95%CI = 3.40, 5.25) and Mismatch conditions ($\beta = 2.19$, 95%CI = 1.43, 3.38).

The Anticipation question did not show any effect of the Cluster, therefore no Bayesian Ordinal Covariance model was applied.

Overall, the anticipation question did not show differences between Clusters, but higher scores in the Match condition than the Mismatch condition. This indicates that both groups could understand the task, correctly perceiving the stimuli and modulate their responses accordingly.

3.3.2. *Sense of agency question*

This is a measure of ‘sense of control’ of an (illusory) action. The null hypothesis is confirmed for the Condition factor ($\beta = 0.20$, 95%CI = −0.22, 0.62, $BF_{10} = 0.3$), for the Limb factor ($\beta = 0.22$, 95%CI = −0.21, 0.67, $BF_{10} = 0.3$) and for the interactions between Cluster and Condition ($\beta = -0.04$, 95%CI = −0.46, 0.40, $BF_{10} = 0.2$), Cluster and Limb ($\beta = -0.15$, 95%CI = −0.58, 0.28, $BF_{10} = 0.3$) and between Cluster, Limb and Condition ($\beta = -0.05$, 95%CI = −0.48, 0.38, $BF_{10} = 0.2$).

The Cluster effect showed the presence of a difference ($\beta = -0.88$, 95%CI = −1.32, −0.44, $BF_{10} > 150$) between the HP ($\beta = 3.38$, 95%CI = 2.30, 4.52) and AHP clusters ($\beta = 5.43$, 95%CI = 4.41, 6.22; See Fig. 5).

Because the analysis showed a $BF_{10} > 3$ for the Cluster effect, the Bayesian Ordinal Covariance model was applied. In this case we confirmed the alternative hypothesis for the Cluster main effect ($BF_{10} > 150$, 95%CI = −1.51, −0.54), but also the interaction between Cluster and Motor Index reached the boundary for the alternative hypothesis ($BF_{10} = 7.6$, 95%CI = −1.37, −0.21). As it is possible to observe in Fig. 6, the Agency – Motricity Index covariance in HP patients showed a negative trend ($\beta = -1.39$, 95%CI = −2.18, −0.62) while in the AHP group the Agency was not covarying with the Motricity Index ($\beta = 0.17$, 95%CI = −0.68, 1.03).

Overall, these results suggest that AHP showed a higher sense of agency than HP for both limbs but that, in HP, sense of agency was modulated by the severity of motor impairment, where aware patients with more severe motor impairment showed higher sense of agency for illusory action with no difference between the plegic and healthy limb.

3.3.3. *Sense of ownership question*

This is a measure of ownership over the ‘examiner’ arm. As in the previous section, we first considered the relationship between the sense of ownership and the degree of awareness and motor impairment of the contralesional limb.

The Bayesian Ordinal Model (Fig. 7) showed that the null hypothesis is confirmed for the Limb factor ($\beta = -0.04$, 95%CI = −0.50, 0.41, $BF_{10} = 0.2$), for the Condition factor ($\beta = 0.18$, 95%CI = −0.27, 0.63, $BF_{10} = 0.3$) and for the interactions between Cluster and Condition ($\beta = 0.06$, 95%CI = −0.42, 0.53, $BF_{10} = 0.3$), Cluster and Limb ($\beta = 0.03$, 95%CI = −0.41, 0.48, $BF_{10} = 0.2$) and between Limb and Condition ($\beta = -0.14$, 95%CI = −0.62, 0.32, $BF_{10} = 0.3$).

The Cluster effect showed the presence of a difference ($\beta = -1.02$, 95%CI = −1.50, −0.55, $BF_{10} > 150$) between the AHP ($\beta = 4.17$, 95%CI = 1.78, 4.16) and HP clusters ($\beta = 2.84$, 95%CI = 1.78, 4.16).

Because the analysis showed a $BF_{10} > 3$ for the Cluster effect, the Bayesian Ordinal Covariance model was applied, showing inconclusive effects for all interactions and main effects involving Personal Neglect ($BF_{10} = 0.4, 0.5$) and Motricity Index (BF10 = 0.5, 0.9), while the Cluster effect confirmed its role ($BF_{10} > 150$). For further details see Supplementary Materials.

These results indicate a difference in the sense of ownership between groups; however, no limb or condition differences were observed and personal neglect or motor impairment effects were not observed.

4. Discussion

The main aim of this study was to investigate sense of agency and ownership for both upper limbs and to explore possible relationship with anosognosia. By means of a vicarious motor paradigm, impaired and healthy limbs could be assessed in similar conditions and we evaluated to what degree 16 right-brain damaged patients experience a possible incongruence of information for illusory motor actions.

Results from the anticipation question allow us to monitor some preliminary aspects for later interpretation of the agency and ownership findings. In the anticipation question, both groups showed a significant condition effect, providing higher ratings when instructions and actions were congruent (match condition) than when they were not (mismatch condition). This suggests that both groups of patients were able to attend to the prime-action relationship. Moreover, group performance for this question was similar, indicating that the criteria adopted for the rating scale were comparable across the two patient groups.

Considering the overall findings for agency and ownership, it seems that patients who are less aware of their motor impairment tended to

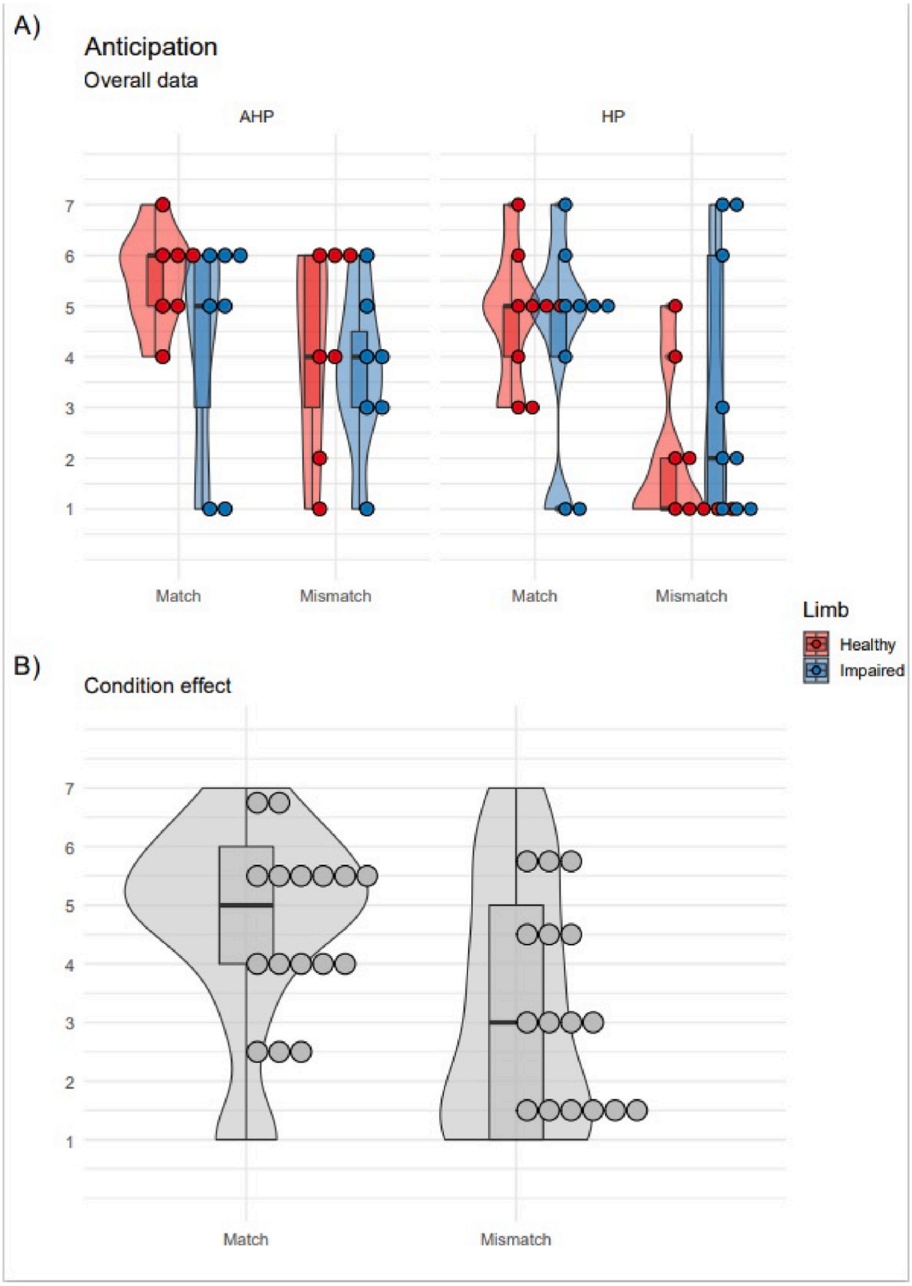

Fig. 4. Raw data representation of the Anticipation question. Violin plots, representing the data distribution, are superimposed to boxplots, indicating the median (the darker line in the middle of the box) the Interquartile Range (the upper and lower boundaries of the box), the non-parametric 95%CI (the whiskers of the boxplots), and the data points represented for each subject with a coloured circle. A) data divided by all factors. B) data representation for the Condition effect.

show a distortion of monitoring for vicarious movements, which was similar for impaired and healthy limbs. This observation suggests that motor comparator processes, also described in the Introduction (Wolpert et al., 1995; Frith et al., 2000; Heilman, 2014), are not restricted to the processing of motor information and their dysfunctions can be caused by right hemisphere lesions despite affecting monitoring of both sides of the body. Our findings are also in line with two previous studies assessing motor monitoring for the healthy limb (Preston et al., 2010; Saj et al., 2014). Saj et al. (2014) reported a distorted but attenuated impact on the healthy limb and the authors claimed that the attenuated impact was due to the differing degree of involvement of the two limbs in the ‘acted’ condition, as hemiplegic patients clearly only attempted to move the paretic limb. In our experiment, both limbs were equally involved in the illusory motor task and we did not observe any relevant difference. Upon first reading, these findings provide even stronger support for the hypothesis that the right-hemisphere network is responsible for agency, ownership and awareness. Moreover, this dominance would also extend when the actions are not performed with one’s own limb but they are vicarious actions.

However, some of our results seem to suggest a more complex explanation. In fact, even if the AHP group showed a higher sense of agency for vicarious movements for both limbs than the HP group, aware patients’ sense of agency was strongly modulated by the severity of their motor impairment. Rather counterintuitively, we observed that HP with more severe motor disorders (i.e., low Motricity Index scores) tended to experience stronger sense of agency for vicarious movements for both limbs. This result suggests that the motor impairment *per se* can modulate the sense of agency not only for the affected limb but also for the healthy limb. This represents an important variable as often studies on anosognosia tend to include patients with complete plegia (e.g. Baier

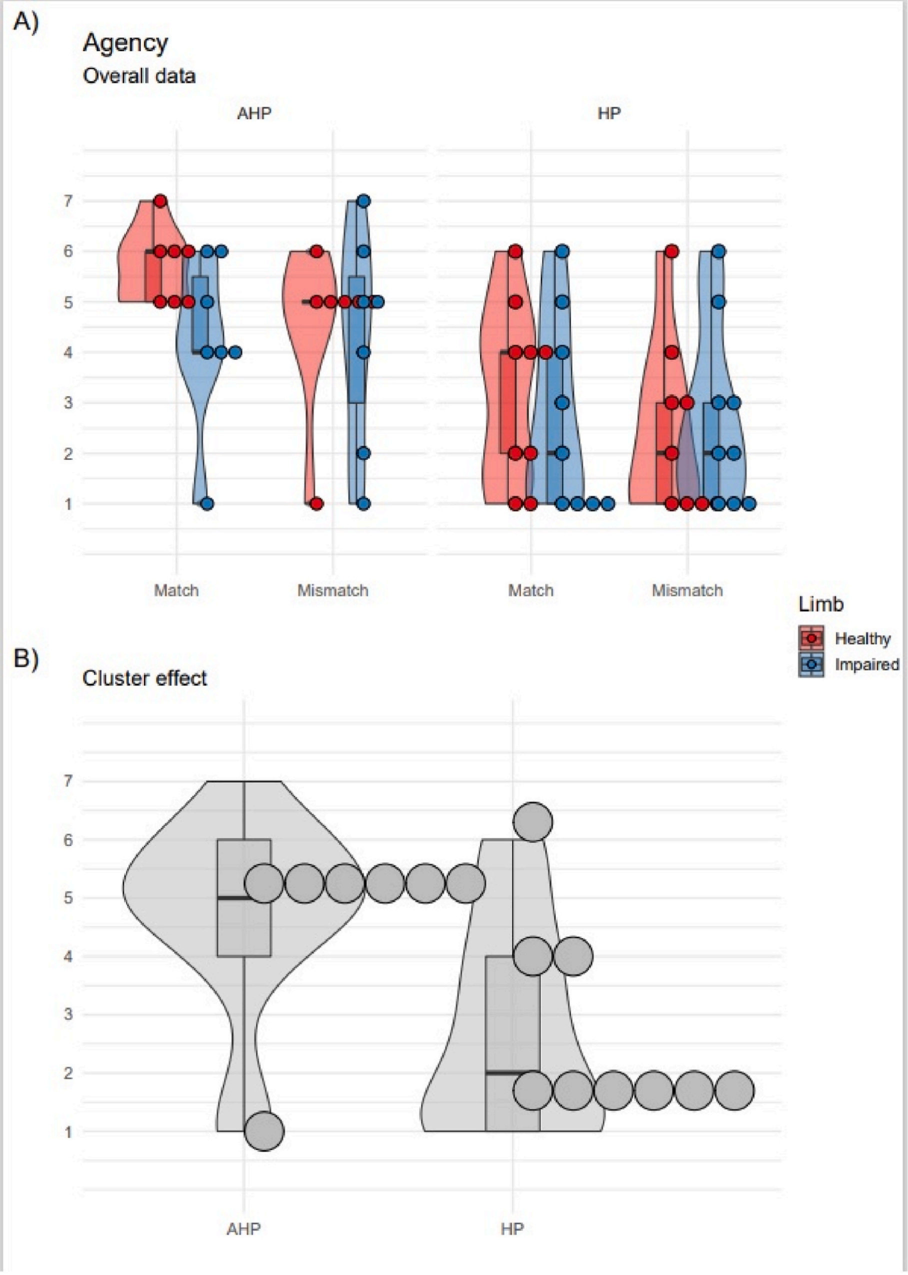

Fig. 5. Raw data representation of the Agency question. A) data divided by all factors. B) data representation for the Cluster effect. For a detailed description, see Fig. 4 caption.

and Karnath, 2008) as this is a pre-requisite to clearly evaluate lack of awareness for motionless limbs with structured interviews (Nathanson et al., 1952).

A possible interpretation, that will certainly need further investigation, is that patients with more pronounced contralesional motor impairment may show some sort of interhemispheric 'compensation' of their impairment by experiencing a higher sense of agency with the intact limb underlying the relevance of interhemispheric connections of motor areas during unilateral actions (e.g., Bloom and Hynd, 2005; Ziemann et al., 1999; Zapparoli et al., 2020). In particular, when healthy participants perform unilateral actions, the ipsilateral motor areas tend to be strongly suppressed via corpus callosum by the increased activity of the contralateral motor areas. Genç et al. (2015) observed a lack of this asymmetric pattern in acallosal patients who showed a less inhibited activity of the ipsilateral limb during unimanual actions (see also Moro et al., 2015 and Pacella et al., 2021 for a review of the literature on this). Interestingly, Gandola et al., 2014 did not find evidence of ipsilateral activation when HP were asked to move their unimpaired limb, suggesting a lack of ipsilateral motor inhibition. Therefore, in hemiplegic patients, the contralesional (intact) motor cortex may lack inhibition input from the lesioned site, resulting in higher activation. This may be linked to the higher sense of agency that we observed for vicarious actions 'performed' with the unimpaired limb, regardless of the degree of awareness.

Considering these results as a whole, it is likely that in case of hemiplegia, lesions do not affect only the contralateral motor abilities, but also has an impact the bilateral balance in the motor network for actions involving both limbs. This may lead, we propose, to a compensatory phenomenon for the healthy side which would result in experiencing a stronger sense of agency for ipsilesional actions as well. Clearly, the extent of this alteration tends to pass unnoticed as hemiplegic patients do not normally show evident difficulties in performing actions

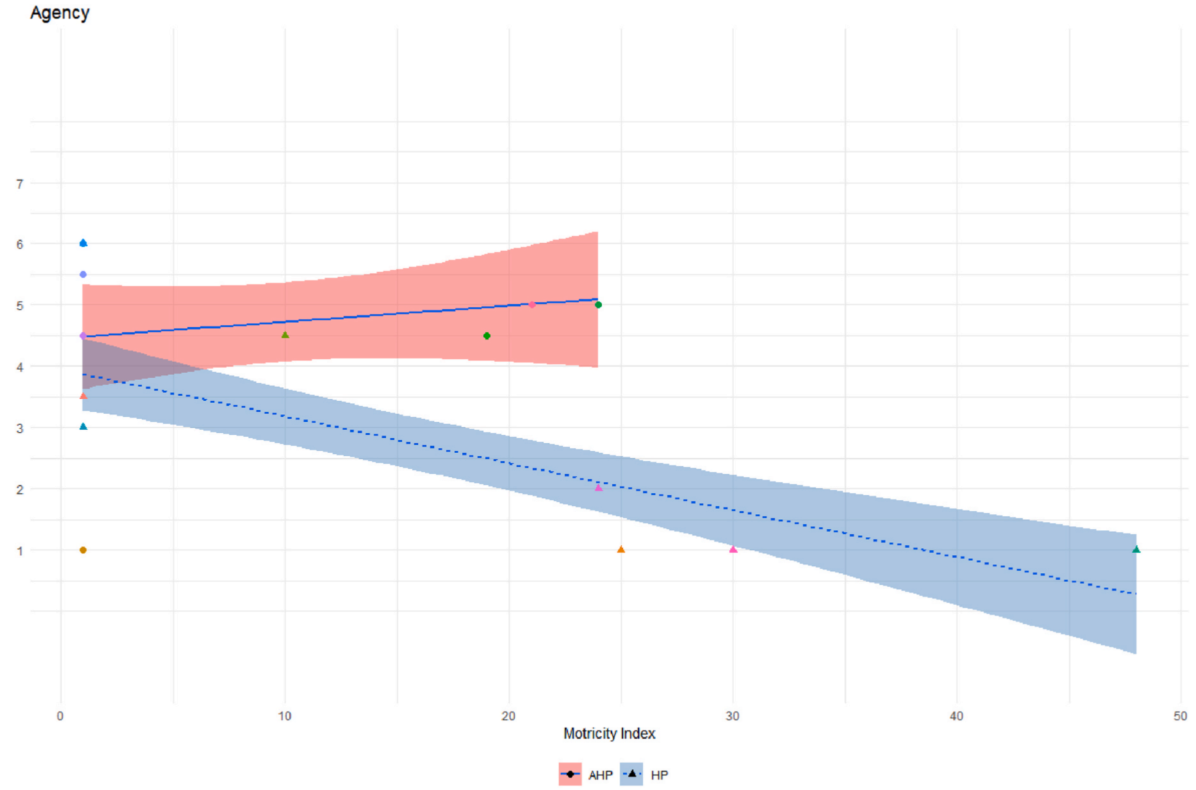

Fig. 6. Raw data representation of the covariation between Agency and Motricity Index score. The circular (if AHP) or triangular (if HP) points are the median for each single patient for the Agency score on the y-axes, while the motricity score is reported on the x-axis. The lines represent the linear model fitting the data, while the coloured shadows are the 95%CI.

with their unimpaired limb; however, it may account for the 'attenuated' distortion of the monitoring process for the unimpaired limb in the event of incongruent feedback, as observed in our study as well as in previous studies (Preston et al., 2010; Saj et al., 2014). In this context, the main hypothesis of a dominant role of the right brain network over awareness for motor monitoring for both limbs appeared supported; however, we cannot ignore that agency for actions on the ipsilesional side also depend on the balance of wider bilateral networks (see Zito et al., 2020 for a meta-analysis) and interhemispheric connections (Bloom and Hynd, 2005; Ziemann et al., 1999). Seghezzi et al.'s (2019) recent study also provides support for a bilateral agency-specific brain network (see also Zapparoli et al., 2020) that would involve the right postcentral gyrus, right superior lobe, left posterior insula and left supramarginal gyrus. Motor impairment and awareness could then conflate and this aspect should be factored in to understand agency mechanisms and anosognosia for motor deficits.

Considering the sense of ownership, AHP showed a significantly higher sense of ownership for the examiner's limb than HP with no difference between limbs. This time the difference was not modulated by other factors such as neglect or degree of motor deficit. This finding supports a tight link between agency and ownership (Baier and Karnath, 2008), but it also suggests that underlying mechanisms of ownership may be less affected by specific motor networks as in the case of sense of agency (Moro et al., 2022).

The lack of effect of neglect in modulating agency and ownership may be due to the method adopted. During the task the examiner minimised the possible impact of neglect by repeatedly addressing the patient's attention to the stimulated side; we cannot exclude that in everyday life the attentional bias may interfere with motor monitoring tasks. Indeed, it should be noted that this is a common situation when testing right-brain damaged patients for evidence of anosognosia, especially if the test requires *hic et nunc* judgments of actions 'performed'. It seems, therefore, that, although neglect may not explain all cases of anosognosia (e.g., Cutting, 1978; Beschin et al., 2012; Rousseaux et al., 2015; Gandola M. et al., 2014), it can still represent an important confounding variable in testing anosognosia (Cocchini et al., 2002; Caggiano and Jehkonen, 2018).

A further consideration concerns the assessment of anosognosia. Our AHP showed significant lack of awareness when asked to evaluate their difficulty to perform bimanual tasks but only a few of them verbally denied the deficit during the initial structured interview. This is a potentially interesting aspect as our group of AHP may represent a qualitative different type of anosognosic patient than those firmly denying their motor impairment despite demonstration. In fact, anosognosia has been defined as a multi-factorial syndrome (e.g., McGlynn and Schacter, 1989; Marcel et al., 2004; Orfei et al., 2007; Vallar and Ronchi, 2006; Vuilleumier, 2004; Cocchini et al., 2010; Moro et al., 2021) and "self-awareness depends on several modular systems" (Heilman, 2014, p. 30). Therefore, it is likely to be due to different causes that may lead, in turn, to different manifestations of unawareness. However, it is interesting to note that these patients also showed a distorted monitoring of vicarious movements even if not all of them vehemently denied their paralysis on the clinical assessment.

The study also presents some limitations. As most of the studies on anosognosia, the limited sample size may have led to false positives or masked some potential findings and null effects should be considered with caution, even though Bayesian Statistics is able to take into account for uncertainty of the measure, reducing the risk of biased results (Gelman et al., 2013). Moreover, the recruitment method has certainly determined the rate of AHP in our sample. Clinicians were instructed to refer patients who appeared to show a reduced awareness for hemiplegia in their initial clinical assessment. Therefore, the relatively high rate of AHP compared to HP should not be surprising and the sample is clearly not representative of clinical population. Moreover, our study leaves some questions unanswered, such as the impact of attentional deficits on processing of sensory (visual) information and direct evidence of

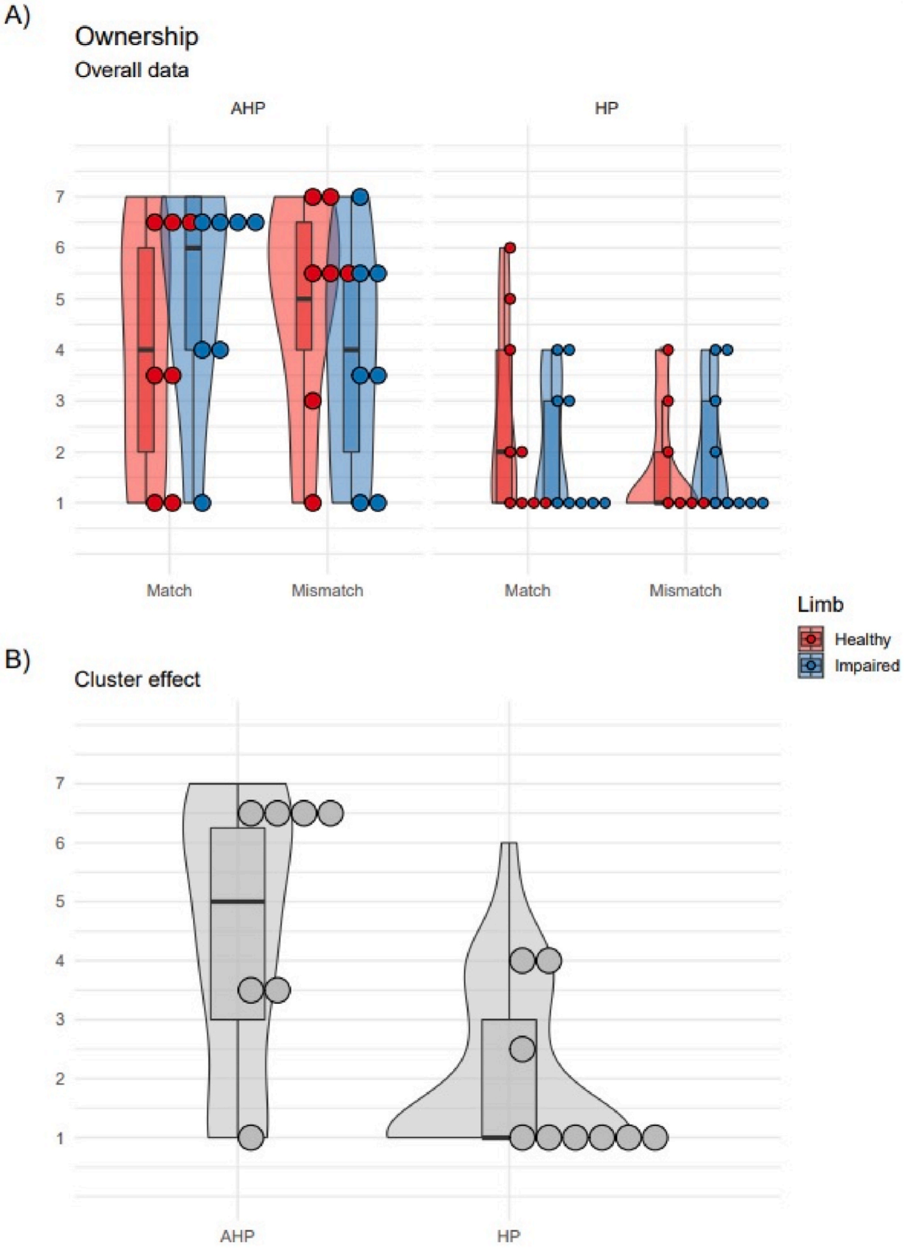

Fig. 7. Raw data representation of the Ownership question. A) data divided by all factors. B) data representation for the Cluster effect. For a detailed description, see Fig. 4 caption.

intention to move, which was not possible to investigate without affecting the illusory phenomenon. A refined paradigm, which may add a direct question about the perceived action, may allow to compare results from both limbs more directly.

To conclude, taking these limitations and our overall results into account, it seems that the monitoring impairment associated with anosognosia is not limited to the contralesional side. It should be considered that the motor impairment *per se* may play a crucial role in the motor monitoring process of the healthy limb by means of a compensatory effect that may be inflated by congruent feedback. Within this framework, while the motor impairment may inflate the sense of agency for action, anosognosia may be associated to inability to account for incongruent feedback, which, in some circumstances, we cannot exclude that it may be linked to attentional deficits.

5. Authors' main contributions

GC, JM, CMC conceived and developed the design of the study. MS ran statistical analyses; VG and AB helped with data acquisition and AB discussed interpretation of findings; GC VM and MS provided main contribution in the writing of the manuscript. All other authors also provided valuable feedback during different phases of the manuscript preparation.

Declaration of competing interest

There are no conflicts of interest.

Data availability

We have provided the link to our data in the Manuscript

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2022.108421.

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