Anosognosia for hemianaesthesia: a voxel-based lesion-symptom mapping study

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A B S T R A C T

Brain-damaged patients affected by hemianaesthesia (i.e., the loss of tactile sensibility on the contralesional side of the body) may deny their deficits (i.e., anosognosia for tactile deficits) even reporting tactile experience when stimuli are delivered on the impaired side. So far, descriptive analysis on small samples of patients reported that the insular cortex, the internal/external capsule, the basal ganglia and the periventricular white matter would subserve anosognosia for hemianaesthesia. Here, we aimed at examining in depth the anatomo-functional nature of anosognosia for hemianaesthesia by means of a voxelwise statistical analysis. We compared two groups of left hemiplegic patients due to right brain damages differing only for the presence/absence of anosognosia for left hemianaesthesia. Our findings showed a lesional cluster confined mainly to the anterior part of the putamen. According to the current anatomical evidence on the neural basis of sensory expectancies, we suggested that anosognosia for hemianaesthesia might be explained as a failure to detect the mismatch between expected and actual tactile stimulation.

1. Introduction

Anosognosia (from the Greek *nosos* disease and *gnosis* knowledge; an-/a-is a negative prefix) is the lack of awareness for neurological/neuropsychological deficits following focal brain lesions. Such a denial behavior has been reported selectively for motor (e.g., hemiplegia), sensory (cortical blindness, hemianopia, hemianaesthesia), and cognitive deficits (see Prigatano, 2010 for a review), and it has been taken as evidence of modality-specific disorders of consciousness. Indeed, when different symptoms are simultaneously present due to a brain damage, patients may be unaware of one of them but aware of another revealing that the monitoring of different aspects of behavior is underpinned by discrete brain mechanisms (see Berti, Làdavas, & Della Corte, 1996 for details on this point).

Within the sensory domain, anosognosia for hemianaesthesia (hereinafter AHA) is diagnosed when patients are

persuaded that they are still able to perceive contralesional tactile stimuli despite the fact that, during the standard neurological examination with eye closed they never report of being touched on the affected side (Bottini et al., 2009; Marcel, 2004; Marcel, Tegnèr, & Nimmo-Smith, 2004; Vallar, Bottini, & Paulesu, 2003, Vallar, Bottini, & Sterzi, 2003). AHA patients may also report an actual tactile sensation when they see a stimulus delivered to their anesthetic body parts (Pia, Garbarini, Fossataro, Fornia, & Berti, 2013; Romano, Gandola, Bottini, & Maravita, 2014). Such a subjective report seems to reflect a real subjective experience of touch rather than a mere verbal confabulation and/or a bias to simply report what is seen, because AHA patients may show normal physiological reactions (i.e., skin conductance response to incoming stimuli delivered to their anesthetic body part; Romano et al., 2014). Interestingly, tactile sensations arise when the physical counterpart is absent (Pia, Garbarini, et al., 2013; Romano et al., 2014).

To the best of our knowledge, only two studies have directly examined AHA (Marcel et al., 2004; Spinazzola, Pia, Folegatti, Marchetti, & Berti, 2008). Both of them demonstrated that when hemianaesthesia (hereinafter HA) co-occur with hemiplegia (i.e., the complete paralysis of the contralesional side of the body; hereinafter HP), AHA can be dissociated from unawareness of HP (hereinafter AHP). In other words, patients can deny their contralesional somatosensory deficits but not their contralesional motor deficits and vice versa. Additionally, Spinazzola and coworkers (Spinazzola et al., 2008) analyzed the individual lesional pattern of four patients affected by AHA reporting that lesions to the insular cortex and to the basal ganglia were crucially associated to AHA (see also (Romano et al., 2014) for similar findings). It was suggested (Spinazzola et al., 2008) that brain damage would impair the ability to distinguish between an internal representation of the sensation and the actual perception of the physical stimulus. The false belief of being still able to perceive tactile stimuli would arise from the intact brain activity within spared areas of the somatosensory system.

In the present paper, we aimed at obtaining a clearer anatomical picture of AHA in order to better understand the nature of the unawareness behavior. As first, we compared the lesional patterns of groups of right brain damaged patients differing only for the presence/absence of AHA. Secondly, on the bases of the anatomical pattern we draw inferences about the functional meaning of the damaged areas.

2. Materials and methods

2.1. Participants

We retrospectively selected the participants of our study from a series of stroke patients with right hemispheric lesions (documented by computerized tomography) and no history of substance abuse/previous neurological diseases, admitted to different rehabilitation centers from 2005 to 2013. The prerequisite to be included in the study was the presence of HA. Additionally, in order to focus exclusively on the neural correlates AHA, patients affected by AHP were not included. As a result, twenty-seven patients (ten women) affected by HA (sixteen with and eleven without AHA), participated in the study approved by the local ethic committee after signing a written informed consent. In order to perform the anatomical comparisons, HA patients were divided into three subgroups: those who suffered from HP (hereinafter HA_HP group; $n = 11$), those who suffered from both HP and AHA (hereinafter AHA_HP group; $n = 11$), and those who suffered from AHA only (AHA group; $n = 5$). The three groups did not differ (Mann Whitney U Test or Student's t test) in terms of age (AHA = mean 69, SD = 7.54; AHA_HP = mean 65.72, SD = 7.86; HA_HP = mean 64.09, SD = 13.41. AHA *vs* AHA_HP, $p = .61$; AHA *vs* HA_HP, $p = .9$; AHA_HP *vs* HA_HP, $p = .73$), educational level (AHA = mean 9.8, SD = 4.6; AHA_HP = mean 8.54, SD = 4.69; HA_HP = mean 10.09, SD = 4.1. AHA *vs* AHA_HP, $p = .46$; AHA *vs* HA_HP, $p = .9$; AHA_HP *vs* HA_HP, $p = .42$) and illness onset (AHA = mean 55, SD = 37.1; AHA_HP = mean 46.63, SD = 12.97; HA_HP = mean 60.27, SD = 33.8. AHA *vs* AHA_HP, $p = .9$; AHA *vs* HA_HP, $p = .65$; AHA_HP *vs* HA_HP, $p = .22$).

2.2. Neurological and neuropsychological assessment

Contralesional visual, motor and tactile deficits were assessed according to a standardized protocol (Bisiach, Pattini, Rusconi, Ricci, & Bernardini, 1997; Bisiach, Vallar, Perani, Papagno, & Berti, 1986) in which scores range from 0 (no deficit) to 3 (severe deficit). What follows is part of the routine neurological diagnosis of HA. Patients blindfolded first receive ten single light touch stimuli applied on the dorsal surface of either the hands or the feet (in random order). They have to report the touch by answering "right" or "left". The score is assigned on the basis of the performance of healthy participants (100% of detections) as follows: score 3 = 3 to 0 stimuli are reported on the contralesional limb; score 2 = 7 to 4 stimuli are reported on the contralesional limb. When patients score 2 (i.e., who reported some contralesional stimuli), they are administered ten double (symmetrical and simultaneous) stimuli ("right", "left" or "right and left" answers). They receive the score 1 if they report 7 to 0 stimuli on the contralesional limb, and 0 if they report 8 to 10.

After the motor and somatosensory examination, AHA and AHP were evaluated according to a standard protocol (Pia, Garbarini, et al., 2013; Romano et al., 2014; Spinazzola, Bellan, Pia, & Berti, 2014). For the diagnosis of AHA, HA patients were first assessed with four questions related to tactile perception (see Spinazzola et al., 2014 for details), two for the upper limb (How is sensation in your arm?, Are you able to perceive a light touch on your left hand?) and two for the lower limb (How is sensation in your leg?; Are you able to perceive a light touch on your left foot?). For each question, HA patients had to rate their own perceptual abilities by means of a verbal judgment: normal perception, perception with difficulties, no perception. Awareness of the potential ability to feel sensations was scored comparing the examiner's judgment with the patient's self-evaluation, as follows: no AHA (score 0, full accord in all questions), moderate AHA (score 1, disagreement in one or two questions), severe AHA (score 2, disagreement in all questions). AHA was diagnosed with score 1 or 2 (0 was the cut-off score since healthy participants and patients without HA do not show any disagreement; Spinazzola et al., 2014).

Additionally, the ability to report tactile stimuli delivered to the affected side was evaluated (yes/no answers) also with eyes open. The same sequence of light touch stimuli applied to both the limbs (ten trials each) of the neurological exam was administered. The discrepancy between the ability to perceive stimuli with open or closed eyes was scored subtracting the number of reported stimuli during the eye closed evaluation from those of the eyes open evaluation as follows: 0 = no positive difference, 1 = difference one to five, 2 = difference five to ten. There was a full high consistency between these scores and those obtained from the interview, namely each participant obtained the same score with the four questions and with the on-line evaluation (i.e., with open eyes).

Handedness was assessed with the Edinburg inventory (Oldfield, 1971), whereas patients' screening for global cognitive functioning was evaluated with the Italian version of the Mini Mental State Examination (Measso et al., 1993). Left extrapersonal and personal neglect were assessed with the behavioral/conventional scales of the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987) and with the Bisiach and co-workers procedure (Bisiach, Perani, Vallar, & Berti, 1986), respectively. The three groups (i.e., AHA, AHA_HP and HA_HP) did not differ (Mann Whitney *U* Test or Student's *t* test) in terms of MMSE score (AHA = 26.03, SD = 2.37; AHA_HP = mean 26.93, SD = 2.81; HA_HP = mean 25.76, SD = 3.2. AHA *vs* AHA_HP, $p = .45$; AHA *vs* HA_HP, $p = .81$; AHA_HP *vs* HA_HP, $p = .37$), BITC score (AHA = mean 94.6, SD = 57.05; AHA_HP = mean 95.36, SD = 48.16; HA_HP = mean 91.18, SD = 50.94. AHA *vs* AHA_HP, $p = .82$; AHA *vs* HA_HP, $p = .94$; AHA_HP *vs* HA_HP, $p = 84$), BITB score (AHA = mean 52.8, SD = 28.22; AHA_HP = mean 51.9, SD = 25.64; HA_HP = mean 49.72, SD = 28.6. AHA *vs* AHA_HP, $p = .95$; AHA *vs* HA_HP, $p = .95$; AHA_HP *vs* HA_HP, $p = .85$) and Bisiach score (AHA mean = 0, SD = 0; AHA_HP = mean 72, SD = 1.1; HA_HP = mean 63, SD = 1.2. AHA *vs* AHA_HP, $p = .15$; AHA *vs* HA_HP, $p = .24$; AHA_HP *vs* HA_HP, $p = .78$) (Demographical, neurological and neuropsychological data of patients are reported in Table 1).

2.3. *Lesion mapping and analysis*

Patients' lesion locations were identified through MRI or CT scans. Lesions were mapped onto the 1 mm^3 MNI 152 standard space through a computerized technique. Image manipulations were achieved with the software MRIcron (Rorden & Brett, 2000). First, the MNI template was rotated on coronal, sagittal and horizontal planes according to the patient's scan angle. Second, a skilled rater (LP), manually mapped the lesion onto each correspondent template slice, whereas a second skilled rater (AP) double-checked for the accuracy of the tracings for each patient (in the only one case of

Table 1 – Demographical, neurological and neuropsychological data. Id = patients' Identification number. Gen = Gender (M = Male, F = Female). Edu = Education (years of formal education). Aet = Etiology (H = hemorrhage, I = ischemia, M = meningioma). Ons = Onset (days between the disease and the first day of the assessment). MMSE = Mini Mental State Examination (0–30). BITC = Behavioral Inattention Test-Conventional subtest (0–146, cut off 129). BITB Behavioral Inattention Test-Behavioral subtest (0–81, cut off 67). Flu = Bisiach test (0–3, cut off 2). Vis = Visual deficits (0–3, cut off 2, the two values refer to the upper and lower quadrant, respectively). Mot = Motor deficits (0–3, cut off 2, the two values refer to the upper and lower limb, respectively). Som = Somatosensory deficits (0–3, cut off 2, the two values refer to the upper and lower limb, respectively). AHA = Anosognosia for hemianaesthesia (0–2, cut off 1, the two values refer to the upper and lower limb, respectively). n.a. = not available.

Id	Group	Age	Gen	Edu	Aet	Ons	MMSE	BITC	BITB	Bisiach	Vis	Mot	Som	AHA
1	AHA	76	F	7	E	51	26.7	134	69	0	1-1	0-0	2-2	1-1
2	AHA	61	M	18	I	26	22.46	140	76	0	3-3	0-0	2-3	1-2
3	AHA	64	M	8	E	23	26.49	17	8	0	0-0	0-0	3-0	2-0
4	AHA	66	M	8	I	115	25.53	132	69	0	3-3	0-0	2-0	1-0
5	AHA	78	M	8	I	60	29	50	42	0	0-0	0-0	3-3	2-2
6	AHA_HP	61	M	4	I	28	20.27	145	81	2	n.a.	3-3	3-3	2-2
7	AHA_HP	65	M	8	I	30	30	133	68	0	0-0	3-3	3-2	0-1
8	AHA_HP	70	F	8	E	60	30	23	16	1	0-0	3-3	3-3	2-1
9	AHA_HP	50	F	18	I	40	29	139	79	0	0-0	3-3	3-3	2-2
10	AHA_HP	82	M	8	I	45	27	89	46	0	0-0	3-3	2-2	2-2
11	AHA_HP	72	F	5	I	60	28	66	60	0	0-0	3-3	3-3	2-2
12	AHA_HP	62	F	8	I	40	28	64	48	0	0-0	3-3	3-3	2-2
13	AHA_HP	64	M	5	I	40	26	141	76	0	0-0	3-3	2-2	2-2
14	AHA_HP	68	M	5	I	70	25	14	1	3	3-3	3-3	3-3	2-2
15	AHA_HP	64	M	17	I	50	25	135	40	2	3-3	3-3	3-3	2-2
16	AHA_HP	65	M	8	I	50	28	100	56	0	0-0	3-3	3-3	2-2
17	HA_HP	66	M	8	E	55	28.53	19	6	0	0-0	3-2	3-3	0-0
18	HA_HP	67	M	8	I	131	26	133	68	0	0-0	3-3	2-0	0-0
19	HA_HP	77	F	17	E	35	28	140	73	0	0-0	3-3	3-3	0-0
20	HA_HP	55	M	5	I	30	17.9	17	8	3	0-0	3-3	3-3	0-0
21	HA_HP	37	F	18	I	50	30	91	53	0	0-0	3-3	3-3	0-0
22	HA_HP	68	M	8	I	30	28	131	79	1	0-0	3-3	2-2	0-0
23	HA_HP	79	F	13	I	112	24	141	80	0	3-3	3-3	3-3	0-0
24	HA_HP	70	F	8	I	70	25	51	37	3	3-3	3-3	3-3	0-0
25	HA_HP	64	M	9	E	41	25	94	45	0	0-0	3-3	3-3	0-0
26	HA_HP	45	M	8	I	72	26	41	20	0	3-3	3-3	3-3	0-0
27	HA_HP	77	F	9	E	37	25	145	78	0	0-0	2-2	3-3	0-0

disagreement, an intersection lesion map was used). Third, the maps were back rotated into the standard space.

We first created two separate lesions overlap, namely AHA_HP and HA_HP groups. Then, we subtracted HA_HP from AHA_HP. The comparison between the two groups was obtained by means of a voxel-by-voxel Liebermeister test ($p < .01$ FDR correction) as implemented in the NPM included in MRIcron (Rorden, Karnath, & Bonilha, 2007).

Second, we put in confront the obtained results with the lesions overlap of the five pure AHA patients (AHA patients without HP). Quantitative estimates of grey and white matter regions involvement were obtained by superimposing the Anatomical Labeling map template AAL (Tzourio-Mazoyer et al., 2002) and the JHU-white matter template (Hua et al., 2008).

3. Results

Fig. 1A and B show the lesion overlapping of AHA_HP and HA_HP groups, respectively, whereas Table 2A and B report their quantitative estimate. The AHA_HP group showed a lesional pattern mainly involving the insula, the caudate nucleus, the posterior limb of internal capsule, the putamen, the superior corona radiata, the superior fronto-occipital fasciculus and the superior longitudinal fasciculus. The HA_HP group displayed a lesional pattern mainly involving the insula, the superior corona radiata and the superior longitudinal fasciculus.

Fig. 1C shows the lesion plot subtraction between the two groups, whereas Table 2C displays its quantitative estimate. The subtraction analysis showed that the anterior limb of the internal capsule, the pallidum, the putamen and the uncinate fasciculus were damaged at least the 50% more frequently in the AHA_HP group respect to HA_HP group. It is worth noticing that the reverse subtraction showed that no regions were injured at least 50% more in the HA_HP, respect to AHA_HP, groups.

The Voxel-by-voxel test comparing the two groups with binomial data (Fig. 2A and Table 3A) revealed a cluster mainly involving the anterior putamen, with a minor involvement of the uncinate fasciculus (and a very small involvement of the pallidum, part of the lentiform nucleus together with the putamen). In the group of five pure AHA patients, the lesional pattern mainly involved the insula, the postcentral gyrus, the rolandic operculum, the superior longitudinal fasciculus, the supramarginal gyrus and the putamen (Fig. 2B and Table 3B).

4. Discussion

With the present investigation, we aimed at finding the neural correlates of anosognosia for hemianaesthesia. By means of a voxelwise statistical analysis, we directly compared HA_HP group lesion plots to AHA_HP group lesion plots. The results were also evaluated in relationship with the lesion plots of a small group of patients affected by a pure form of AHA (i.e., patients affected by unawareness of the

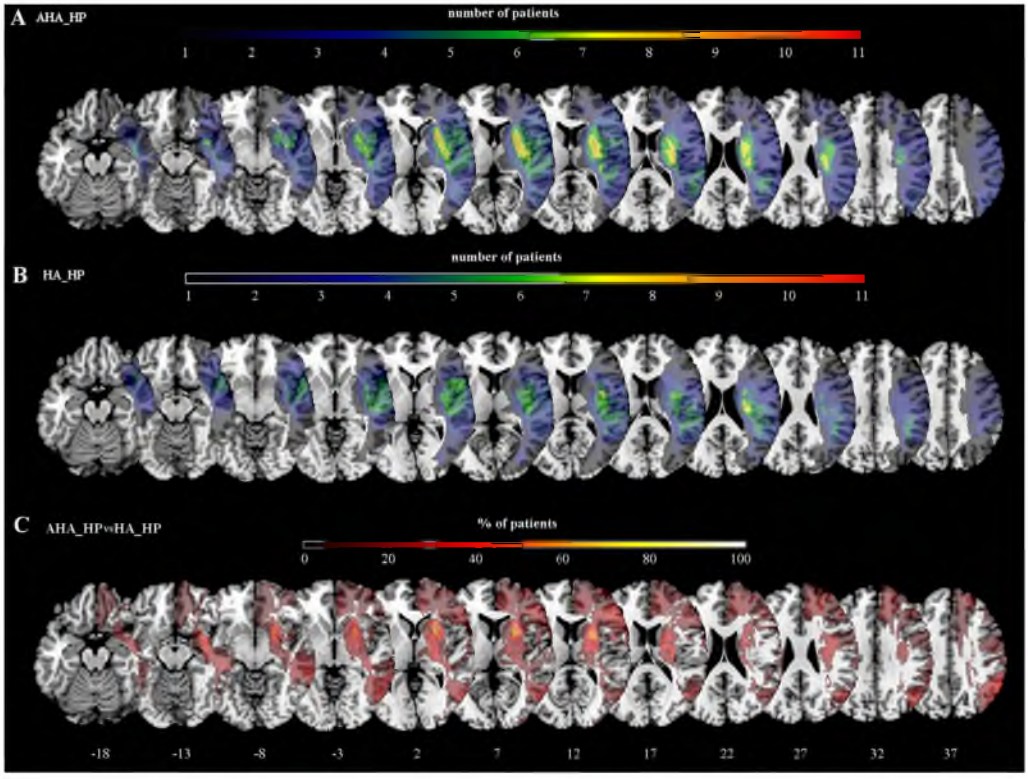

Fig. 1 – Overlays of regional lesion plots of the AHA_HP (A) and HA_HP (B) groups. The frequency is represented trough a color scale ranging from black (lesion in one patient) to red (lesion in eleven patients). Subtraction of regional lesion plots (C). Regions damaged more frequently in the AHA_HP group respect to HA_HP group are displayed in warm colors, from dark red to white. MNI coordinates of each transverse section are reported.

Table 2 – Quantitative estimate of the regional lesion plots of the AHA_HP (A) and the HA_HP groups (B). Region overlaps in three patients or more in at least one of the two groups are reported. For each region, the percentage of lesioned voxels (Region %), the number of patients (Patients #) and MNI coordinates are reported, Quantitative estimate of the subtraction of regional lesion plots (C). Only brain regions that were damaged the 50% or more frequently in the AHA_HP group respect to HA_HP group are reported. For each region, the number of lesioned voxels (Voxels %), the percentage of lesioned voxels (Region %), the percentage of patients (Patients %) and MNI coordinates (MNI) are reported.

Grey/White matter	(A) AHA_HP					(B) HA_HP				
	Region %	Patients #	MNI			Region %	Patients #	MNI		
			X	Y	Z			X	Y	Z
Amygdala	67	5	31	0	−12	8	2	36	3	−25
Angular	93	5	42	−50	22	77	5	42	−50	22
Anterior_cor_rad	79	6	23	20	5	33	4	25	22	9
Anterior_limb_int_cap	92	7	22	7	13	71	4	21	−5	18
Calcarine	0	0	0	0	0	18	3	28	−69	6
Caudate	54	8	21	4	21	44	5	20	−12	21
Fornix	21	3	30	−16	−10	0	0	0	0	0
Frontal_Inf_Ope	95	6	39	17	5	97	6	48	12	0
Frontal_Inf_Orb	85	4	46	19	−12	77	5	52	19	−9
Frontal_Inf_Tri	89	5	46	21	0	87	5	47	19	3
Frontal_Mid	82	4	49	43	11	40	2	41	41	3
Frontal_Sup	80	3	24	48	23	14	2	30	3	47
Heschl	100	7	42	−16	6	100	6	41	−21	5
Hippocampus	21	4	36	−21	−6	3	2	35	−19	−8
Insula	100	9	31	−17	16	99	8	31	−16	20
Occipital_Inf	3	2	49	−74	−3	8	3	33	−81	0
Occipital_Mid	77	4	49	−67	25	80	3	33	−80	0
Occipital_Sup	22	3	34	−71	41	0	0	0	0	0
Olfactory	43	3	26	9	−12	0	0	0	0	0
Pallidum	100	7	28	−4	−3	56	3	28	−3	−5
Parietal_Inf	92	4	52	−48	38	31	3	37	−50	38
Postcentral	83	4	53	−6	25	68	5	60	−16	19
Posterior_corona_rad	30	7	27	−24	20	39	7	29	−24	23
Posterior_limb_int_cap	86	8	26	−11	18	55	6	26	−12	16
Posterior_tha	29	3	37	−52	−3	62	3	27	−72	5
Precentral	85	5	37	3	29	70	3	58	10	16
Putamen	100	9	24	6	4	84	6	36	1	−2
Retrolenticular_part	66	5	26	−21	2	42	3	37	−34	5
Rolandic_Oper	100	7	38	−4	13	98	7	42	−2	10
Sagittal_stratum	57	5	43	−28	−10	27	2	39	−18	−9
Superior_corona_rad	88	9	29	−18	20	77	8	27	−18	21
Superior_fronto-occi_fas	95	8	21	7	20	100	4	17	−6	19
Superior_long_fas	100	8	30	−4	19	100	8	31	−16	22
SupraMarginal	91	5	47	−42	22	76	6	46	−35	29
Temporal_Inf	46	4	56	−16	−18	30	3	53	−6	−27
Temporal_Gyurus_Mid	92	5	48	−8	−18	88	5	46	0	−16
Temporal_Pole_Mid	78	4	47	3	−17	75	5	52	15	−22
Temporal_Pole_Sup	89	6	44	4	−17	87	6	54	9	0
Temporal_Gyrus_Sup	94	7	41	−14	3	95	7	43	−9	−5
Thalamus	55	6	22	−19	13	20	3	22	−18	6
Uncinate_fasc	92	6	33	2	−14	0	0	0	0	0

Grey/White matter	(C) AHA_HP minus HA_HP				
	Region %	Patients %	MNI		
			X	Y	Z
Anterior_limb_int_cap	86	55	22	7	13
Pallidum	100	64	22	6	1
Putamen	98	73	24	12	0
Uncinate_fasc	92	55	33	2	−14

tactile impairment without any motor deficits). Our results showed that the anterior part of the putamen, and, to a much less extent the uncinate fasciculus and pallidum, seem to be crucial for the emergence of anosognosia for hemianaesthesia.

As we mentioned above, so far only two studies reported data about the neural basis of anosognosia for hemianaesthesia (Romano et al., 2014; Spinazzola et al., 2008). Both of them employed the traditional overlay lesion plot technique on small samples of patients. Specifically, Spinazzola and coworkers

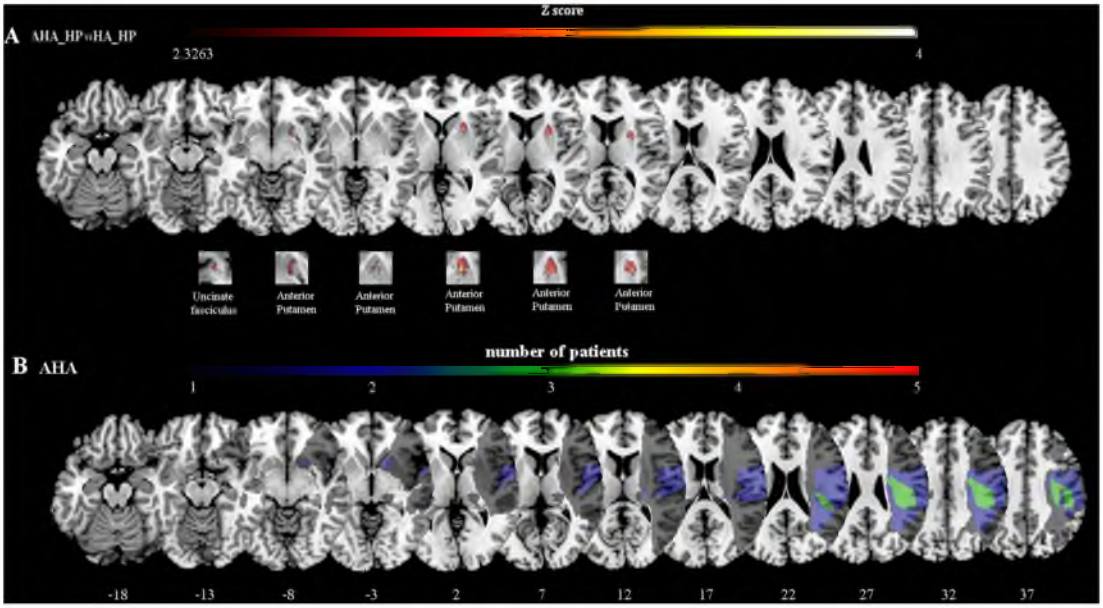

Fig. 2 – (A) Brain regions significantly associated to AHA (AHA_HP group *vs* HA_HP group). All voxels which survived to the binomial test are displayed. The color scale represents Z-Libermesiter scores. (B) Overlays of regional lesion plots of the AHA group. The frequency is represented trough a color scale ranging from black (lesion in one patient) to red (lesion in five patients).

(Spinazzola et al., 2008) analyzed the lesion overlap of four AHA patients. They found that all patients had in common lesions to the putamen, the insular cortex, the internal and the external capsule. Similarly, Romano and coworkers (Romano et al., 2014) analyzed the lesional pattern of five AHA patients and reported that four had lesions to the insular cortex, the basal ganglia and the periventricular white matter. It is worth noticing that Spinazzola and coworkers (Spinazzola et al., 2008) suggested also a preliminary explanation of tactile unawareness on the basis of the interpretation of unawareness for motor deficits. It has been suggested that anosognosia for hemiplegia is a domain specific disorder of monitoring voluntary actions. A damage to the cortical network subserving motor awareness in the lateral premotor (Berti et al., 2005; Vocat, Staub, Stroppini, & Vuilleumier, 2010) or insular (Berti et al., 2005; Fotopoulou, Pernigo, Maeda, Rudd, & Kopelman, 2010; Karnath, Baier, & Nagele, 2005; Moro, Pernigo, Zapparoli, Cordioli, & Aglioti, 2011; Vocat et al., 2010) cortex (but see also Fotopoulou et al., 2010 for a prevalence of basal ganglia damages), would prevent distinguishing between intended and actual movement execution, leading to unawareness of the deficit. Additionally, a spared activity of the brain structures that implement the intention-programming system (see Heilman, Barrett, & Adair, 1998 for the first motor intentional theory of AHP) would induce the patients' false belief of being still able to move (Garbarini & Pia, 2013; Garbarini, Piedimonte, Dotta, Pia, & Berti, 2013; Pia et al., 2013). Accordingly, Spinazzola and coworkers (Spinazzola et al., 2008) proposed that in AHA the brain damage would prevent to distinguish between an internal representation of the sensation arising from expectations/previous experience of tactile perception and the real actual perception of the physical stimulus. The false belief of being still able to perceive tactile stimuli might then arise from the intact brain activity of the spared areas within the somatosensory system. As for the denial of motor deficit, the false belief would be caused by an actual neural signal.

Differently from the small samples of the two above-mentioned studies, here we employed a lesion subtraction technique on larger samples of patients. With respect to the overlay lesion plot technique, this approach can identify the neural correlates of a given behavior by comparing the overlay lesion plot of patients with, and patients without, the deficit of interest. In other words, if groups differ only for the critical deficit, the method is able to distinguish between structures that are only often damaged from structures that are specifically required for the function of interest (Rorden et al., 2007). Accordingly, we retrospectively selected patients affected by HA with or without AHA (but no AHP). It is worth noticing that the groups on which we performed anatomical comparisons did not differed in terms of socio-demographic and the other neuropsychological measures. Hence, each variable, except AHA, were balanced among groups. Our anatomical results are consistent with previous literature (Romano et al., 2014; Spinazzola et al., 2008). However, they suggest that a specific structure, namely the anterior putamen, could be the neural basis for the emergence of AHA.

Traditionally, the putamen has been subdivided into two distinct regions, namely the anterior part, more connected with the premotor cortex and the anterior cingulate cortex, and the posterior part, more linked to the sensorimotor cortex and the cerebellum (e.g., Alexander, DeLong, & Strick, 1986; Fernandez-Seara, Aznarez-Sanado, Mengual, Loayza, & Pastor, 2009). Alteration of the anterior putamen functioning has been associated to different diseases. Dyskinesias, for instance, have been linked to a significant density decrease of the dopamine D2 receptors within the anterior putamen

Table 3 – (A) Quantitative estimate of the brain structures significantly associated to AHA (AHA_HP group *vs* HA_HP group). For each brain structure, the number of clustering voxels, z score, and MNI coordinates of the center of mass are reported. Quantitative estimate of the regional lesion plots of the AHA group (B). Region overlaps in at least three patients or more are reported. For each region, the percentage of lesioned voxels (Region %), the number of patients (Patients #) and MNI coordinates are reported.

Grey/White matter	(A) AHA_HP *vs* HA_HP				
	Region %	z score	MNI		
			X	Y	Z
Putamen	17	3.58	24	12	0
Pallidum	1	3.2	22	6	1
Uncinate_fasciculus	8	2.83	33	2	−14
Grey/White matter	**(B) AHA**				
	Region %	Patients #	MNI		
			X	Y	Z
Angular	55	2	40	−57	22
Anterior_limb_int_cap	42	2	13	11	−5
Caudate	19	2	13	11	−9
Frontal_Inf_Ope	85	2	62	14	4
Frontal_Mid	37	2	32	2	36
Heschl	99	2	43	−17	5
Insula	92	3	37	−28	22
Occipital_Mid	20	2	34	−62	33
Pallidum	47	2	14	10	−4
Parietal_Inf	67	2	44	−45	38
Postcentral	71	3	51	−21	31
Posterior_cor_rad	35	2	30	−50	19
Posterior_limb_int_cap	43	2	24	−22	10
Precentral	37	3	40	−14	36
Putamen	91	2	16	14	−10
Rectus	4	2	19	15	−11
Retrolenticular_part	48	2	25	−24	10
Rolandic_Oper	97	3	42	−34	22
Superior_corona_rad	53	3	30	−13	24
Superior_long_fas	96	3	32	−19	24
SupraMarginal	71	3	46	−36	23
Temporal_Mid	35	2	41	−57	21
Temporal_Pole_Sup	11	2	56	5	−3
Temporal_Sup	76	3	51	−38	22
Thalamus	18	2	23	−23	11

(Nadeau, Couch, Devane, & Shukla, 1995). Reduced volume of the anterior putamen has been reported in Huntington's disease (Bohnen et al., 2000) whereas reduced density seems to subserve cognitive impairments often observed in spinocerebellar ataxia (Braga-Neto et al., 2012). Surface abnormalities of the anterior putamen have been reported in teenagers with Attention Deficit Hyperactivity Disorder (Biederman et al., 2008). The anterior putamen has been found to be involved in different functions: selection of voluntary movements (Gerardin et al., 2004), motor learning (Miyachi, Hikosaka, Miyashita, Karadi, & Rand, 1997), reasoning (Melrose, Poulin, & Stern, 2007) cognitive/visuomotor skill-learning, (Beauchamp, Dagher, Aston, & Doyon, 2003; Floyer-Lea & Matthews, 2004), cognitive "shift"(McClure, Berns, & Montague, 2003) and general attention (Romo, Scarnati, & Schultz, 1992).

Interestingly, the anterior putamen seems to be involved also in prediction errors (O'Doherty et al., 2004), including error responses to the unexpected absence of input (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009). Accordingly, a recent fMRI study (Langner et al., 2011) reported that anterior putamen was activated by the omissions of expected sensory stimuli, tactile, auditory or visual (indeed, further activations of the posterior putamen were thought to reflect motor preparation, rather than sensory expectations). Additionally, expectancies of tactile stimuli leaded to increased activities in the somatosensory cortices and deactivations in visual/auditory cortices. These data suggest that the brain represents tactile-specific information within both the somatosensory and other sensory domains in order to prioritize the elaboration of the specific stimuli and optimize the detection before the target event occurs. Then, the brain compares specificity of the expectations with the specificity of the actual stimulation and the anterior putamen would subserve omission-related Bayesian surprise according to the specificity of the predictions (Langner et al., 2011). Interestingly, this idea is reminiscent of a recent interpretation of AHP in terms of imbalances between actual experiences of the body and prior expectancies of body signals (Fotopoulou, 2014, 2012).

On these bases, we propose a possible interpretation of anosognosia for hemianaesthesia. Tactile-specific expectancies would be generated within spared somatosensory cortices. Interestingly, the overlays of regional lesion plot of both AHA_HP (Fig. 1A and Table 2A) and AHA (Fig. 2B and Table 3B) groups showed that these structures were intact or at least partially spared. The subsequent comparison between expectancies and (absence) of perceived stimuli would not be possible due to anterior putamen lesions. Accordingly, this part of the putamen is the main brain structure emerging from the comparison between AHA_HP and HA_HP groups (Figs. 1C and 2A, Table 2C and 3A). Indeed a minor involvement was reported also for the uncinate fasciculus. Interestingly, these fiber tract has been related to impaired error monitoring during visual location of objects (Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011). The anterior putamen was also damaged in two AHA patients (Fig. 2B, Table 3B). The consequences of not being able to detect the mismatch between an expected tactile sensation and its actual absence would lead patients to rely entirely on their tactile sensory expectancies (i.e., reporting tactile stimuli in absence of tactile perception) developing a false belief of being able to feel the stimuli (see also Pia, Cavallo, & Garbarini, 2014).

We must clearly acknowledge that our interpretation is still at speculative level. Direct neuroimaging evidence (e.g., fMRI or EEG) of activities during the expectancies of tactile stimuli are barely required in order to strengthen our conclusions. Additionally, future studies should also obtain more in depth data about somatosensory processing as, for instance, tactile threshold/discrimination when stimuli are delivered or not delivered, proprioception, pain perception and so on. Finally, in our sample of hemianaesthesic patients with a pure form of anosognosia, the anterior putamen was clearly damaged in two patients (out of five). Although CT scan can highly underestimate the extent of the subacute disruptive effects produced by a stroke on the areas surrounding the lesion (e.g., anterior putamen) or "hide" functional diaschisis (e.g., between spared somatosensory areas and anterior putamen), we certainly need to collect more cases of pure AHA in

order to have a full anatomical account of anosognosia for hemianaesthesia.

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