**Motor Versus Body Awareness: Voxel-based Lesion Analysis in Anosognosia for Hemiplegia and**

**Somatoparaphrenia Following Right Hemisphere Stroke**

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Large study on the neuroanatomy of motor anosognosia versus body disownership

Subcortical involvement is necessary for body and motor awareness

‘Up-to-date’ motor awareness may also rely on cortical processing

**\*Manuscript**

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Running Head: Lesions Affecting Motor and Body Awareness

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4 **Motor Versus Body Awareness: Voxel-based Lesion Analysis in Anosognosia for Hemiplegia and**

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**Abstract**

1

2 Anosognosia for hemiplegia (AHP) is informative about the neurocognitive basis of motor

3

4 awareness. However, it is frequently associated with concomitant symptoms, such as hemispatial

5

6 neglect and disturbances in the sense of body ownership (DSO). Although double dissociations

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8 between these symptoms have been reported, there is ongoing debate about whether they are

9 manifestations of independent abnormalities, or a single neurocognitive deficit. We aimed to

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11 investigate the specificity of lesions associated with AHP by surpassing four, existing

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13 methodological limitations: (a) recruit a relatively large sample of patients (total N = 70) in a multi-

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15 centre study; (b) identify lesions associated with AHP in grey and white matter using voxel-based

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17 methods; (c) take into account the duration of AHP and concomitant neglect symptoms; and (d)

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19 compare lesions against a control hemiplegic group , patients suffering from AHP and DSO, and a

20

21 few, rare patients with selective DSO. Results indicated that acute AHP is associated with a wide

22

23 network, mainly including: (1) the Rolandic operculum, (2) the insula and (3) the superior temporal

24

25 gyri. Subcortically, damage mainly involved the basal ganglia and white matter, mostly the

26

27 superior corona radiate, arcuate fasciculus and the part of the ventral, superior longitudinal

28

29 fasciculus. Persistent symptoms were linked with wider damage involving fronto-temporal cortex

30

31 and long white matter tracts. A shift in the latero-medial direction (mainly involving the basal

32

33 ganglia and surrounding white matter) emerged when DSO was taken accounted for. These results

34

35 suggest that while bodily awareness is processed by areas widely distributed across the brain,

36

37 intact subcortical structures and white matter tracts may be necessary to support basic feelings of

38

39 owning and controlling contralateral body parts. An accurate and ‘up-to-date’ awareness of our

40 motor abilities, however, may rely also on intact processing in cortical areas which presumably

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42 allow higher-order inferences about the current state of the body.

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48 **Keywords:** Motor Awareness; Body Awareness; Anosognosia for hemiplegia; Sense of Body

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50 ownership; Voxel-Based Lesion Mapping.

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54 **Introduction**

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56 Human bodily awareness entails the processing, integration and re-representation of one’s

57

58 sensorimotor states as one’s *own bodily states*. However, bodily awareness is as vulnerable as it is

59

60 complex, as demonstrated by the variety of disturbances caused by a range of clinical (e.g.

amputation, deafferentation, brain damage) and experimental (multisensory conflicts) factors

1

2 (Fletcher & Fotopoulou, 2015; Pernigo et al., 2012; Ramachandran & Rogers-Ramachandran, 2000;

3

4 Scandola et al., 2014). In terms of central neurological damage, right hemisphere stroke can cause

5

6 severe disorders of bodily awareness, such as anosognosia (from the Greek, α = without, νό σος =

7

8 disease, γ νώ σις = knowledge) for hemiplegia (AHP). AHP has been described as the denial of motor

9 paralysis contralateral to a brain lesion (Babinski, 1914). In this condition, hemiplegic patients may

10

11 state that they are able to move their paralysed limbs, to walk, or carry out daily life activities

12

13 without needing help. Sometimes they also behave or attempt to act as if they really can move

14

15 their body normally (e.g. Moro, Pernigo, Zapparoli, & Cordioli, 2011). Not surprisingly, AHP in the

16

17 acute stages following stroke is associated with poor long-term functional outcome (Gialanella &

18

19 Mattioli, 1992; Hartman-Maeir, Soroker, & Katz, 2001), even if in most cases it resolves

20

21 spontaneously, days or weeks post-stroke (Pia, Neppi-Modona, Ricci, & Berti, 2004; Vocat, Staub,

22

23 Stroppini, & Vuilleumier, 2010).

24

25 Although the syndrome includes several clinical forms and many concomitant symptoms,

26

27 such as personal and visuospatial neglect (Jenkinson, Preston, & Ellis, 2011), there is ongoing

28

29 debate about whether these are manifestations of independent abnormalities, a single primary

30

31 deficit, or a combination of deficits (see Jenkinson & Fotopoulou, 2014). Recent, integrated

32

33 clinical, experimental and neuroimaging approaches (Cocchini, Beschin, Fotopoulou, & Della Sala,

34

35 2010; Fotopoulou, Pernigo, Maeda, Rudd, & Kopelman, 2010; Gandola et al., 2014; Moro et al.,

36

37 2011; Vocat et al., 2010) have shown the limits of theories which explain AHP as the result of

38

39 single deficits such as sensory, spatial, attentional or metacognition abnormalities (see also

40 Prigatano, 2010 for a review). Indeed, recent multifactorial theories suggest that AHP is a multi-

41

42 component syndrome that may be caused by a collection of disturbances (Davies, Davies, &

43

44 Coltheart, 2005; Marcel, Tegnér, & Nimmo-Smith, 2004; Mograbi & Morris, 2013; Vuilleumier,

45

46 2004) and their dynamic relations (Fotopoulou, 2014; Fotopoulou, 2012; Jenkinson & Fotopoulou,

47

48 2014).

49

50 This perspective is consistent with the fact that, apart from a more frequent occurrence

51

52 after right than left-hemisphere damage (e.g. Cocchini, Beschin, Cameron, Fotopoulou, & Della

53

54 Sala, 2009 for left hemisphere cases; Jehkonen, Laihosalo, & Kettunen, 2006), recent

55

56 neuroimaging studies have not identified a consistent pattern of brain lesion or dysfunction

57

58 selectively associated with AHP. Specifically, some studies have highlighted the potential role of

59

60 cortical areas such as the right insula in AHP (Berti et al., 2005; Fotopoulou et al., 2010; Karnath,

Baier, & Nägele, 2005; Vocat et al., 2010). The insular cortex has been more generally implicated in

1

2 body ownership, perceived agency and interoceptive representations of body states (Craig, 2009;

3

4 Karnath et al., 2005; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). Other cortical areas selectively

5

6 associated with AHP are the right premotor and the inferior frontal cortex, in particular

7

8 Broadmann’s areas 6, 44/45 and 47 (Berti et al., 2005; Fotopoulou et al., 2010; Kortte et al., 2015),

9 which are involved in motor initiation, preparation and monitoring. However, there are conflicting

10

11 results between these studies regarding which areas of the frontal operculum are implicated in

12

13 AHP (Berti et al., 2005; Kortte et al., 2015) and other studies fail to find a selective role for

14

15 premotor areas and the inferior frontal gyrus in AHP (Karnath et al., 2005). In addition, some but

16

17 not all studies report that lesions involving subcortical structures such as the thalamus, the basal

18

19 ganglia and the amygdala-hippocampal complex may relate to certain behavioural facets of AHP

20

21 (Fotopoulou et al., 2010; Moro et al., 2011; Vocat et al., 2010, see Table 4 for a review of previous

22

23 studies).

24

25 In addition to intrinsic limitations of lesion mapping studies (Rorden, Fridriksson, &

26

27 Karnath, 2009; Rorden & Karnath, 2004), part of the aforementioned differences between studies

28

29 may be attributed to different sample sizes and selection criteria, including criteria for diagnosis,

30

31 subtype of anosognosia, age, lesion size, perfusion patterns, white matter involvement, and the

32

33 time interval since stroke for both diagnosis and neuroimaging examination (Karnath et al., 2005;

34

35 Kortte et al., 2015; Vocat et al., 2010). Unfortunately, addressing all these limitations in a single

36

37 study is currently unfeasible for most labs. Accordingly, in the current study we wished to address

38

39 at least four of these considerations. Specifically, we aimed to: (a) recruit a relatively large sample

40 of patients with a clear diagnosis of severe AHP (verified by two, separate interviews); (b) examine

41

42 identifiable lesions in grey *and white matter*, while (c) also taking into account the duration of AHP

43

44 and concomitant neglect symptoms. Finally, we aimed to (d) compare the lesions of AHP patients

45

46 not only to a control group showing hemiplegia without anosognosia (HP group) but also to

47

48 another group of patients whose anosognosia was accompanied by body ownership disturbances.

49

50 Clinical dissociations between AHP and body ownership disturbances have been described since

51

52 Gerstmann’s seminal paper (1942) on the topic. The critical difference seems to be that while AHP

53

54 affects patients’ awareness of action, right hemisphere stroke can also cause abnormalities in

55

56 awareness of one’s body parts as one’s own. For example, patients with asomatognosia show a

57

58 lack of recognition regarding the existence or ownership of their limbs (Vallar & Ronchi, 2009).

(somatoparaphrenias; Gerstmann, 1942), such as the belief that the affected limb belongs to

1

2 another person, including friends, relatives or even the examiner. Typically, somatoparaphrenia is

3

4 regarded as a positive or productive variant of asomatognosia (in the Jacksonian sense; Jackson,

5

6 1932), and it may take several clinical forms (reviewed by Vallar & Ronchi, 2009), but the particular

7

8 application of terms like asomatognosia and somatoparaphrenia remains debated. To escape this

9 terminological ambiguity in this paper, we follow Karnath and colleagues (Baier & Karnath, 2008)

10

11 in classifying all abnormal feelings and beliefs regarding the existence and ownership of one’s

12

13 limbs as ‘disturbed sensation of limb ownership” (DSO).

14

15 AHP and DSO have been found to co-occur frequently (Vallar & Ronchi, 2009) and previous

16

17 studies have suggested a strong link between the sense of limb ownership and action awareness,

18

19 and common critical lesions in the posterior insular cortex (Baier & Karnath, 2008). However,

20

21 more recent, in depth neuropsychological examinations have demonstrated the possibility of

22

23 behavioural and neural dissociations between AHP and DSO (Gandola et al., 2012; Invernizzi et al.,

24

25 2013; Vallar & Ronchi, 2009a). Specifically, certain ‘pure’ cases of DSO (i.e. patients that did not

26

27 show any indications of AHP) have been identified and their lesions have been compared with

28

29 cases of pure AHP (Invernizzi et al., 2013; albeit the AHP patients were recruited as part of a

30

31 previous study, Berti et al., 2005), or mixed AHP (Gandola et al., 2012). These studies have

32

33 revealed that, contrary to AHP (Berti et al., 2005; Kortte et al., 2015), DSO is not selectively

34

35 associated with damage to the inferior frontal gyrus, including the lateral premotor cortex and

36

37 instead it seems to involve critical lesions to grey subcortical structures and white matter bundles

38

39 (see also Zeller, Gross, Bartsch, Johansen-Berg, & Classen, 2011). Taken together, the conflicting

40 results of previous studies, as well as the frequent co-occurrence of AHP and DSO, warrant a

41

42 specific examination of the relation between DSO and AHP. In the current study we used a voxel-

43

44 based, lesion comparison approach (Kimberg, Coslett, & Schwartz, 2007; Rorden & Karnath, 2004;

45

46 Rorden, Karnath, & Bonilha, 2007) to test the hypothesis that at least partially segregated

47

48 networks are damaged in AHP and DSO, involving more cortical premotor and insular grey matter

49

50 areas in the former, and subcortical white and grey matter structures (basal ganglia and white

51

52 matter tracts around them) in the latter.

53

54

55

56 **2. Materials and Methods**

57

58

A total of 70 patients with damage to the right hemisphere were consecutively recruited (in each

1

2 center) from three different, collaborating centers: the acute, stroke rehabilitation unit at the St.

3

4 Thomas’s Hospital in London, acute stroke and stroke rehabilitation wards at the (former)

5

6 University Hospital of North Staffordshire, and the Rehabilitation Ward of the Sacro Cuore Hospital

7

8 (Negrar, Verona, Italy) over a period of 5 years (from 2006 to 2011). Behavioural, experimental

9 data for 31 of the current anosognosic patients and 23 of the controls have been previously

10

11 described in case studies (Besharati, Kopelman, Avesani, Moro, & Fotopoulou, 2015; Fotopoulou

12

13 et al., 2011; Jenkinson, Haggard, Ferreira, & Fotopoulou, 2013), or small sample group studies

14

15 (Jenkinson, Edelstyn, Drakeford, & Ellis, 2009, AHP N = 10; Jenkinson, Edelstyn, & Ellis, 2009, AHP

16

17 N = 8; Fotopoulou et al., 2010, AHP N = 7; Moro et al., 2011, AHP N = 12). In this study, the clinical

18

19 and anatomical data of 70 patients were analyzed. Unfortunately, further screening data is not

20

21 available/informative for our sample, due to the practical and ethical considerations regarding

22

23 recruitment and the time intervals involved (see also below). For instance, as stated above,

24

25 patients were recruited from units that admitted and cared for patients at different intervals and

26

27 durations post stroke. In addition, in one of the three centres the researchers did not have access

28

29 to the medical records but rather it was the responsibility of clinicians to refer patients meeting

30

31 the inclusion criteria below, based on their clinical observations.

32

33 Patients were eligible if they had (i) a stroke-induced right-hemisphere lesion as confirmed

34

35 by clinical neuroimaging; (ii) contralateral upper limb plegia (they were unable to move their left

36

37 arm). Exclusion criteria were: (i) previous history of neurological or psychiatric illness; (ii)

38

39 medication with severe cognitive or mood side-effects; (iii) severe language, general cognitive

40 impairment, or mood disturbance that precluded completion of the study assessments.

41

42 For all recruitment centres, the presence or absence of AHP and DSO was diagnosed by

43

44 means of the same criteria (scores of 1 or 2 on the Berti AHP interview; clear clinical indications of

45

46 anosognosia, and clear indications of DSO in a body ownership interview, see below for details).

47

48 Based on these assessments, patients were categorized into four different groups: 1. Patients with

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50 Anosognosia for Hemiplegia (AHP Group, N = 25 patients); 2. AHP patients that also showed DSO

51

52 (AHP+DSO Group, N = 13 patients); 3. pure DSO patients (DSO Group, N = 4 patients); 4. Control

53

54 patients with hemiplegia but no body awareness symptoms (HP Control Group, N = 28 patients).

55

56 When possible (for 36 out of 42 target patients), unaware patients were examined in a follow-up

57

58 assessment in order to investigate the persistence of AHP and DSO in sub-acute and chronic stages

considerations, we conducted lesion comparisons (see below) on the basis of a single time cut-off:

1

2 i) AHP patients who recovered awareness within 40 days (AHPacute only subgroup, N = 6) and ii)

3

4 those who continued to show body unawareness symptoms after 40 days from stroke (AHPchronic

5

6 subgroup, N = 14). These analyses were exploratory as the two groups of chronic and ‘acute only’

7

8 patients were unequal in number. Most papers typically refer to anosognosia as a transient

9 phenomenon that tends to recover spontaneously days or weeks after onset. However, the

10

11 available data in the literature on the evolution of AHP are actually mixed; less than 20% of

12

13 published studies involve follow-up assessments and there is no specification of optimal

14

15 timeframes for the characterization of patients as acute versus chronic. Most studies consider the

16

17 presence of AHP to be chronic if it is present at a post onset interval greater than one month, 40

18

19 days, three months or six months (see Nurmi & Jehkonen, 2014 for the most recent and

20

21 systematic review on the issue). Our selection was therefore within this range, based on our

22

23 experience of the time intervals that patients are likely to be admitted and remain available for

24

25 testing and follow-up assessments in the various clinical units involved. The ratio between acute

26

27 and chronic patients therefore reflects merely this fact. Furthermore, we found that DSO was still

28

29 present after 40 days in 11 AHP+DSO patients, and in all the pure DSO patients. Therefore, we did

30

31 not further sub-divide these groups. All patients gave written informed consent and the research

32

33 was conducted in accordance with the guidelines of the Declaration of Helsinki (2013) and

34

35 approved by the Local Ethical Committees of each centre.

36

37

38

39 *2.2. Assessment of AHP and DSO*

40 The diagnosis of AHP was ascertained by means of a structured interview (Berti, Làdavas, & Della

41

42 Corte, 1996), including general questions regarding the consequences of stroke (e.g., ‘How is your

43

44 left arm? Can you move it?’) and confrontation questions (e.g. ‘Please, touch my hand with your

45

46 left hand. Have you done it?’). In this interview full acknowledgement of paralysis is scored as ‘0’,

47

48 while denial of the paralysis despite acknowledging not having reached for the examiner’s hand is

49

50 scored as ‘1’; and a score of ‘2’ is given when patients denied both motor impairments and the

51

52 failure in reaching for the examiner’s hand. We considered patients as anosognosic when they

53

54 scored 1 or 2, as in previous studies (e.g. Berti et al., 1996; Fotopoulou et al., 2008, 2010).

55

56 We also used a second measure of AHP, namely the frequently used scale by Bisiach and

57

58 colleagues (Bisiach, Vallar, Perani, Papagno, & Berti, 1986)*.* In this 4-point scale, if the disorder is

score is ‘0’ = no anosognosia; ‘1’ is scored if the disorder is reported only following a specific

1

2 question about the strength of the patient’s limbs; ‘2’ is scored if the disorder is acknowledged

3

4 only after demonstration; and finally ‘3’ is scored if no acknowledgement of the disorder can be

5

6 obtained. We considered patients as anosognosic when they scored 2 or 3 (Karnath et al., 2005;

7

8 Orfei et al., 2007).

9 This double assessment of AHP allowed us to repeat the assessment, and in this way to

10

11 take into account the potential variability of AHP symptoms in time and in relation to the context

12

13 of the questioning (Marcel et al., 2004; Vocat & Vuilleumier 2010; Fotopoulou et al., 2010; Moro

14

15 et al., 2011). Examining patients’ diagnosis in this manner, we found no discrepancies in the

16

17 classification of patients based on these two assessments, thus confirming the validity of our

18

19 classification. For the purposes of behavioural analyses of neuropsychological performance (see

20

21 below), each patient’s scores on the two scales were converted into percentages and averaged to

22

23 form a composite index of anosognosia. This composite score further allowed us a range of scores

24

25 that could better capture the clinical variability of AHP and thus be better suited to further

26

27 analyses with other behavioural deficits that are multicomponent and determined by more than

28

29 one assessment (e.g. neglect).

30

31 Somatoparaphrenia (DSO) was assessed by means of a standardized, ad-hoc procedure.

32

33 Patients were preliminary asked to identify their right and left hands. If they failed to identify their

34

35 left hand spontaneously, they were asked to look at their left hand and respond to a series of

36

37 questions: “What is this? Who does this hand belong to? How many hands do you have? Is this

38

39 your hand? Where is your left hand? Finally, the ‘One-item test’ was administered; we asked

40 patients to reach and touch their left hand with the right one (Bisiach et al., 1986). Patients were

41

42 included in the groups of DSO or AHP+DSO when presented with delusional beliefs about the

43

44 contralesional side of their body, in particular when they denied that the arm belonged to them

45

46 and/or attributed it to somebody else in at least two of these questions. Bizarre, persistent and

47

48 refractory-to-correction explanations of patients delusion were recorded (Feinberg, Venneri,

49

50 Simone, Fan, & Northoff, 2010). In the AHP+ DSO group these symptoms were associated with

51

52 denial of arm paralysis as identified with interviews described above. By contrast, the ‘pure DSO’

53

54 patients, although insisting that the left arm did not belong to them, were able to describe its

55

56 paralysis accurately in the above interviews and they never claimed being able to move ‘their own

57

58 left arm’, or behaved accordingly.

*2.3. Neurological and neuropsychological assessment*

1

2 Motor deficits were assessed by means of a standardised evaluation (Bisiach et al., 1986) which

3

4 score ranges from 0 (no deficit) to 3 (severe deficit), and all patients showed a severe

5

6 contralesional hemiplegia (score 3/3 for both upper and lower limbs). Hand-dominance was

7

8 assessed by a questionnaire (Oldfield, 1971). Abstract reasoning was assessed by ‘Similarities’

9 tasks (Italian version: Appollonio et al., 2005; British version: Wechsler, 1997; sub-test of Wechsler

10

11 Adult Intelligent Scale, WAIS-III; statistical comparisons for each target group were performed only

12

13 with regards to the HP group patients tested with each version). Extrapersonal neglect was

14

15 assessed by the line cancellation, star cancellation, figure and shape copying subtest of the

16

17 Behavioural Inattention Test ((Wilson, Cockburn, & Halligan, 1987). The scores of all patients on

18

19 each test were then calculated in percentages and averaged to form a composite index of neglect

20

21 (see also Vocat et al., 2010). The ‘Comb/Razor test’ (McIntosh, Brodie, Beschin, & Robertson,

22

23 2000) was used for the assessment of personal neglect.

24

25

26

27 *2.4. Lesion Analysis*

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29

30

31 *2.4.1. Lesion Mapping and Voxel-based Comparisons*

32

33 The cerebral lesions were documented in 49 subjects via computerised tomography (CT) and in 21

34

35 subjects via magnetic resonance imaging (MRI). Lesions from these scans were segmented and co-

36

37 registered using a manual procedure. Lesions were outlined by two of us (SP and VM) who were

38

39 blind to each scan’s group classification. In the case of disagreement of two lesion plots, the

40 opinion of a third, expert anatomist was requested. Scans were registered to the T1-weighted MRI

41

42 scan template (ICBM152) of the Montreal Neurological Institute, furnished with the MRIcron

43

44 software (ch2, [http://www.cabiatl.com/mricro/mricron/index.html).](http://www.cabiatl.com/mricro/mricron/index.html))

45

46 First, the standard template (size: 181 × 217 × 181 mm, voxel resolution: 1 mm2) was

47

48 rotated on the three planes in order to match the orientation of the patient’s MRI or CT scan.

49

50 Lesions were outlined on the axial slices of the rotated template. The resulting lesion volumes

51

52 were then rotated back into the canonical orientation, in order to align the lesion volumes of each

53

54 patient to the same stereotaxic space. Finally, in order to exclude voxels of lesions outside white

55

56 and gray matter brain tissue, lesion volumes were filtered by means of custom masks based on the

57

58 ICBM152 template.

The lesion volumes of the different groups were compared by using Rorden’s Non-

1

2 Parametric Mapping (NPM) software (Rorden et al., 2007). Voxel-based lesion comparisons were

3

4

5 performed in order to contrast the lesion patterns of the various clinical groups. In all these

6

7

8 comparisons of lesions between groups (with the exception of neglect comparisons, see below),

9

10 we used non-parametric analyses with dichotomic data. This was necessary as data on DSO were

11

12

13 dichotomous (i.e. evidence of disturbances of somatic ownership or not) and the distribution of

14

15 scores in control patients is by definition very limited.

16

17

18 We used a non-parametric implementation (based on the Liebermeister (L) measure) of a

19

20 two-group comparison on a binary variable that has proved to be more sensitive than chi-squared

21

22

23 or Fisher’s Exact test in situations without fixed marginals (Phipps, 2003; Rorden et al., 2007). Only

24

25

26 voxels lesioned in at least 30% of the patients were included in the analysis, in order to maximize

27

28 the power of analysis and avoid spurious results (Kimberg et al., 2007; Medina, Kimberg,

29

30

31 Chatterjee, & Coslett, 2010). This means that lesioned voxels that overlapped in at least 8 patients

32

33 for the comparison of the two larger groups (HP vs. AHP groups), and at least 4 patients for the

34

35

36 comparison of AHP+DSO with HP patients were included. No thresholds were used for the DSO

37

38

39 group because of the small number of patients (i.e., 4 patients; this limitation is acknowledged in

40

41 the interpretation of the results). The binomial voxel-based lesion mapping test was then

42

43

44 subjected to permutation by using the NPM software, in order to determine a critical L cut-off (at

45

46 *p* < .05), based on 5000 random permutations of the data (Kimberg et al., 2007). Finally, maps of

47

48

49 voxels with L-score intensity were generated and only the voxels that survived to the critical L

50

51 value for each group comparison were considered. In the statistical group comparisons that

52

53

54 involved the single, small group of pure DSO patients, results were corrected for multiple

55

56

57 comparisons using a 1% false discovery rate (FDR).

58

59 For each main lesion comparison a power map was generated and only voxels with power

voxel of the power map, area under ROC curve (AUROC) scores were provided, ranging between

1

2 0.5 (minimum power) to 1 (maximum discrimination power).

3

4 In addition to the above main analyses, as aforementioned we also conducted exploratory

5

6 analyses on patients with ‘acute only’ versus ‘chronic’ AHP and we also conducted a separate,

7

8 Voxel Lesion Symptom Mapping Analysis (VLSM, Rorden et al., 2007) on the continuous scores of

9 the composite index for the spatial neglect. This t-test based analysis allowed us to explore the

10

11 lesion sites associated with hemispatial neglect, irrespective of group classification (see Kimberg et

12

13 al., 2007 for rationale of this approach). However, as our behavioural results revealed that

14

15 patients with AHP had more neglect than control patients, we also conducted the same analysis

16

17 only in patients with AHP to examine the patterns of lesions associated with neglect specifically in

18

19 this population. In these t-test statistics, only voxels lesioned in more than 20% of the patients

20

21 were used, the critical cut-off for the t-test being set at *p*=0.5, correcting for FDR. The results of

22

23 these analyses are reported in the Supplementary Materials.

24

25

26

27 *2.4.2. Brain regions and tracts classification*

28

29 Three anatomical templates furnished with MRIcron served to identify gray and white matter

30

31 region labels: the “automated anatomical labeling” (AAL) template (Tzourio-Mazoyer et al., 2002),

32

33 the JHU white-matter tractography atlas, (Mori, Wakana, Zijl, & Nagae-Poetscher, 2005), and the

34

35 “NatBrainLab” template of the “tractography based Atlas of human brain connections Projection

36

37 Network” (Natbrainlab, Neuroanatomy and Tractography Laboratory) (Catani & Thiebaut de

38

39 Schotten, 2012; Thiebaut de Schotten et al., 2011). The results regarding the superior fronto-

40 occipital fasciculus that emerged from the JHU atlas have not been reported, because, according

41

42 to current understanding, this fasciculus does not exist in humans. The JHU atlas predated this

43

44 debate and wrongly indicated this structure (see debate Schmahmann et al., 2006 vs. Forkel et al.,

45

46 2014).Voxel intensity values of the Natbrainlab templates (http://www.natbrainlab.com) were

47

48 converted to 16 bit when different, and thresholded at a probability > 50% (i.e., voxels in which

49

50 more than 50% of the population studied have the same tract) in order to consider only the almost

51

52 invariable anatomical core of each single tract and not its periphery (Thiebaut de Schotten et al.,

53

54 2011).By superimposing the significant lesion patterns on the anatomical templates we calculated

55

56 the number of lesioned voxels (i.e., the amount of volume in mm3) and the centre of gravity

57

58 (centre of mass) for each region.

**3. Results**

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4 *3.1. Behavioural Results*

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8 *3.1.1. Demographics and Neuropsychological Performance*

9 Socio-demographic characteristics and scores on neurological and neuropsychological tests are

10

11 shown in Table 1. By means of independent samples t-test and Mann-Whitney statistics

12

13 (Bonferroni corrected for multiple comparison), demographics and the composite scores on

14

15 neuropsychological tests of the target groups were compared to each other and to those of the

16

17 controls. Spearman correlation coefficients were used to examine potential associations between

18

19 neglect scores and degree of anosognosia within each group. Results are summarised in Table 1

20

21 (demographics and comparisons with the control group) and in the text below. Due to the small

22

23 sample of the DSO group (N = 4; 2 men and 2 women, mean age 63 ± 3 years) only exploratory

24

25 comparisons have been performed; results of the later comparisons are described in the text

26

27 below.

28

29 Mean age was 66 years (± 12). Patients were examined either in the acute (< 10 days, 19

30

31 patients), subacute (from 11 to 40 days, 23 patients) or the chronic phase (> 40 days, 28 patients)

32

33 (see Table 1). The groups did not differ in age, interval from onset, gender (but AHP vs. HP, *p* =

34

35 .04), chronicity and handedness ratios.

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41

42 *Table 1 about here*

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50 *3.1.2. Anosognosia for hemiplegia.*

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52 All control subjects and all the DSO patients scored 0 (no anosognosia) in the anosognosia

53

54 composite index. By contrast, as expected anosognosia scores in the AHP and the AHP+DSO

55

56 groups were significantly higher than zero (Table 1; Wilcoxon signed-rank test, both *p*s < 0.01).

than ‘pure’ AHP patients (i.e. they showed more anosognosia), this difference did not reach

1

2 significant levels (see Table 1).

3

4

5

6 *3.1.3. Neglect*

7

8 For extrapersonal neglect the analysis of the composite index (0%: no neglect, 100%: maximum

9 neglect) indicates the presence of more neglect in both AHP and AHP+DSO groups with respect to

10

11 HP group (All *p*s < 0.01; see Table 1). Nevertheless, the degree of anosognosia did not correlate

12

13 with extrapersonal neglect (*r*(36) = -0.08, *p* = 0.67) in the AHP group (*r*(24) = -0.17, *p* = 0.45) or the

14

15 AHP+DSO group (*r*(12) = 0.32, *p* = 0.3165). There was no significant difference between the AHP and

16

17 AHP+DSO groups (see Table 1). Finally, the pure DSO patients (Mdn =59%; Interquartile Range =

18

19 18%) showed less symptoms of neglect than AHP and AHP+DSO patients (*U*(38) = 31, *Z* = 1.87, *p* <

20

21 0.031), with an average performance comparable to HP patients (*U*(30) = 36, *Z* = 1.17, *p* = 0.12).

22

23 The groups showed a similar pattern of results on personal neglect. Personal neglect was

24

25 significantly worse in the AHP+DSO group with respect to HP controls (all *p*s < 0.01; see Table 1),

26

27 while there was no difference between AHP and HP controls and between the AHP and AHP+DSO

28

29 groups (see Table 1). Personal neglect did not correlate with the degree of anosognosia (*r(*31) = -

30

31 0.07, *p* = 0.69) in the AHP (*r*(23) = -0.19, *p* = 0.38), nor in the AHP+DSO group (*r*(8) = 0.43, *p* = 0.29).

32

33 Although the difference was not statistically significant, DSO patients (Mdn = 0; Interquartile

34

35 Range = 0.56) tended to perform better relative to AHP+DSO patients (*U* = 27, *Z* = 1.87, *p* = 0.07).

36

37 There was no statistically significant difference between the DSO group and AHP patients (*U* = 63,

38

39 *Z* = 1.1, *p* = 0.27), or the control HP group (*U* = 58, *Z* = 0.11, *p* = 0.93).

40

41

42 *3.1.4. Executive functions*

43

44 The AHP and the AHP+DSO groups performed worse in comparison to the HP group (all *p*s < 0.05;

45

46 see Table 1) on the Similarities task, but there was no difference between the two target groups

47

48 (see Table 1).

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50

51

52

53

54 *3.2. Lesions Associated with Anosognosia*

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56

In order to find lesions specifically associated with AHP in the acute phase (irrespective of

1

2 whether the symptoms would spontaneously recover or not – see below), we compared the

3

4 lesions of the AHP group (25 patients) with the lesions of the HP group (28 patients; see Table 2,

5

6 first column). A lesion cluster was centered on the subcentral gyrus (Naidich et al., 2004), reaching

7

8 the dorsal part of the right insula (Figure 1.A, axial plane Z=19) and extended cortically to the

9 adjacent ventral premotor cortex, involving a small part of both the parietal and frontal

10

11 operculum. It also encompassed the Heschl and temporal superior gyrus, but spared the primary

12

13 somatosensory and primary motor cortex. Subcortically, it extended to the tracts of the superior

14

15 corona radiata and external capsule, and reached the more dorsal part of the caudate nucleus.

16

17 Significant voxels were also found in the superior longitudinal fasciculus (SLF). According to the

18

19 white matter atlas of the Natbrainlab laboratory (Catani & Thiebaut de Schotten, 2012; Thiebaut

20

21 de Schotten et al., 2011), significant voxels were present on the cortico-spinal tract, internal

22

23 capsule, and the arcuate fasciculus, in particular in the anterior segment. This segment is known to

24

25 run next to the ventral part of the superior longitudinal fasciculus (or SLF III) and connects parietal

26

27 with frontal regions (Martino et al., 2013; Thiebaut de Schotten et al., 2011).

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31 *-----------------------------------------------------------*

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33 *Figure 1 and Table 2 about here*

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35 *-----------------------------------------------------------*

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39 *3.2.2. Transient versus lasting anosognosia: AHPacute only and AHPchronic vs HP*

40 In order to investigate the differences in lesions between patients who showed anosognosia in

41

42 both the acute and chronic stages (>40 days; *AHPchronic; N = 14*) with those who recovered

43

44 awareness within 40 days (*AHPacute only’ N = 6)*, we compared the lesions of the two groups of AHP

45

46 patients (*AHPacute only and AHPchronic separately*) with all the HP controls, using the same criteria and

47

48 statistical methods as for the other main comparisons (as described in Methods). As shown in

49

50 Table 2 (middle and right columns) results indicate that patients who remain anosognosic in the

51

52 chronic phase present with more cortical lesions, involving ventral premotor cortex and the

53

54 temporal superior cortex. Nevertheless, lesions also extend to the subcortical white matter, in

55

56 particular to the cortico-spinal tract (corresponding to superior corona radiate in JHU atlas),

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2 *3.3. Lesions associated with Anosognosia versus with Body Ownership Disturbances*

3

4 In 13 out of our 28 AHP patients, anosognosia was concomitant with disturbed sensations of limb

5

6 ownership (DSO). This gave us the opportunity to investigate potential different lesional correlates

7

8 of the two syndromes in two ways. Firstly, by means of indirect comparisons, we compared

9 patients with both AHP and DSO (AHP+DSO) against the HP control group to examine qualitatively

10

11 how this difference compared with the one above between the pure AHP patients and the HP

12

13 controls (section 3.2.1). In a separate analysis of the same rationale, we also added the four

14

15 “pure” DSO patients into the AHP+DSO group to see how their difference from controls compared

16

17 with the results of section 3.2.1. Secondly, by means of direct comparisons, we then compared the

18

19 patients with AHP+DSO against the pure AHP group. This set of analyses allowed us to explore the

20

21 potential patterns of lesions differently correlated to the two syndromes and in relation to control

22

23 hemiplegic patients.

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25

26

27 *3.3.1. Indirect Comparisons*

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29 *3.3.1.1. AHP+DSO vs. HP*

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31

32 When compared to HP controls, AHP+DSO was associated only with subcortical lesions in basal

33

34 ganglia and white matter (Table 3, first column). Significant voxels were located in the putamen,

35

36 the caudate (only one voxel), and surrounding tracts of the internal capsule. Similarly, the

37 NatBrainLab atlas showed significant voxels in the internal capsule, with additional significant

38

39 voxels in the cortico-spinal and cortico-pontine tracts, and a small cluster in the arcuate fasciculus.

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47 *Table 3 about here*

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54 *3.3.1.2. AHP+DSO and DSO vs. HP*

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56 When we add the four patients affected by pure DSO to the above lesion analysis (i.e. AHP+DSO,

amount of significant voxels increases, in particular in the caudate nucleus. In the JHU atlas the

1

2 superior corona radiate emerges while in the Natbrainlab atlas an additional significant cluster of

3

4 lesion emerges in the white matter tracts of the corpus callosum.

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6

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8 *-----------------------------------------------------------*

9 *Figure 2 about here*

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11 *-----------------------------------------------------------*

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16 *3.3.2 Direct comparisons between pure AHP and mixed AHP and DSO groups (AHP vs. AHP+DSO)*

17

18 The direct comparison of lesions involved in AHP vs. the AHP+DSO Groups (and vice versa) did not

19

20 show any significant results in our sample. Therefore, in explorative analyses with limited

21

22 explanatory power (please see Discussion), we investigated the results of the same voxel-based

23

24 lesion comparisons by using less restrictive criteria. All voxels were included in the comparison

25

26 (not only voxels lesioned in at least 30% of the patients), and a less restrictive correction criteria

27

28 was used (1% False Discovery Rate).

29

30 We found that AHP+DSO patients showed lesions in the thalamus, caudate and pallidum

31

32 more frequently than AHP. Moreover, the subcortical damage, especially in the posterior white

33

34 matter tracts, appeared more evident (Figure 3A, Table 3, third column), with the JHU atlas

35

36 reporting significant voxels in the anterior capsule and in two small clusters in superior

37 longitudinal fasciculus and posterior thalamic radiations, and the Natbrainlab atlas reporting

38

39 significant voxels in the cortico-spinal tract, the corpus callosum and the fornix. On the other hand,

40

41 patients with isolated AHP showed more frequent lesions only in 16 voxels in the amygdala in

42

43 comparison to patients with AHP+DSO (Figure 3B, Table 3, last column). This minimal result and

44

45 the absence of any higher order cortical areas is not surprising given the fact that both groups in

46

47 this comparison showed AHP, and the additional presence of DSO seems to be associated mostly

48

49 with subcortical lesions (see above). Finally, according to the JHU, but not to the Natbrainlab atlas,

50

51 there was a significant cluster in the capsule. Natbrainlab atlas indicated the involvement of the

52

53 anterior commissure, the inferior longitudinal fasciculus, the inferior occipito frontal fasciculus,

54

55 the optic radiations and the uncinate.

56

57 *-----------------------------------------------------------*

1

2 Taken together, indirect and exploratory direct comparisons of lesions involved in anosognosia

3

4 (AHP) versus disturbed sensations of limbs ownership (DSO) indicate a shift of damage from more

5

6 cortical regions (mainly involved in AHP) towards subcortical structures, such as basal ganglia and

7

8 thalamus, and the surrounding white matter, which are principally involved in DSO.

9

10

11 *3.3.3. Supplementary Lesion Analyses*

12

13 Further analyses regarding: 1) the comparison of all patients suffering from body awareness

14

15 disorders (AHP and AHP+DSO) versus HP; 2) the explorative analyses of the ‘pure’ DSO small group

16

17 versus all the other groups (AHP, AHP+DSO and HP); and 3) the lesional correlates of neglect are

18

19 reported in the Supplementary Materials. In brief, the first two sets of these analyses provided

20

21 further support for the finding that the lesions associated with pure AHP are more cortical and

22

23 lateral than those associated with either pure DSO, or a combination of body awareness disorders.

24

25 Finally, the third analyses showed that the critical set of lesions associated with visuospatial

26

27 neglect differs from that associated with AHP, DSO and their combination.

28

29

30

31 **4. Discussion**

32

33 The main purpose of the study was to investigate in a relatively large sample of patients (N = 70)

34

35 the patterns of lesions associated with anosognosia for hemiplegia (AHP) and their potential

36

37 specificity in relation to the lesions associated with the hemiplegia itself, as well as with

38

39 concomitant disordered feelings of body ownership (DSO). In addition, we were interested in

40 exploring the pattern of lesions associated with other manifestations of the syndrome such as

41

42 symptom duration and neglect.

43

44 Our results indicate that while acute AHP is associated with damage to several cortical and

45

46 subcortical areas, there is specific involvement of three principal cortical areas around the

47

48 subcentral gyrus: (1) the Rolandic operculum (ventral premotor cortex), (2) the insula and (3) the

49

50 Heschl and superior temporal gyri. In addition, damage was observed subcortically, mainly in the

51

52 basal ganglia, while white matter lesions seemed to affect mostly the superior corona radiate, and

53

54 the external capsule. According to the white matter atlas of the Natbrainlab laboratory (Catani &

55

56 Thiebaut de Schotten, 2012; Thiebaut de Schotten et al., 2011), significant lesions were present on

57

58 the cortico-spinal tract and the anterior segment of the arcuate fasciculus, in a region next to the

al., 2011; Martino et al, 2013). Furthermore, in acute AHP, damage to the insula and basal ganglia

1

2 seemed crucial, but for the persistence of the symptom beyond 40 days, wider damage involving

3

4 fronto-temporal cortex and long white matter tracts seemed necessary. A shift in the latero-

5

6 medial direction (and mainly involving the basal ganglia) emerged when DSO co-occurred with

7

8 AHP (relative to HP controls), although direct comparisons between the pure AHP and the mixed

9 AHP+DSO groups did not reveal any significant differences, possibly due to the smaller samples

10

11 involved. However, the potential role of the basal ganglia and their connections with cortical areas

12

13 in DSO was confirmed by exploratory (i.e. using less restrictive criteria) direct comparisons

14

15 between the pure and the mixed AHP groups, as well as the lesion patterns of four rare patients

16

17 suffering from pure DSO. These results are discussed in turn below.

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19

20

21 *4.1. Lesion Patterns Associated with Anosognosia for Hemiplegia*

22

23 The large sample of anosognosic patients analysed in this study (N = 38) permits us to confirm and

24

25 expand the crucial role that certain cerebral structures and tracts have in motor awareness (see

26

27 table 4). Specifically, our study confirms the involvement of both the insular cortex (Berti et al.,

28

29 2005; Fotopoulou et al., 2010; Karnath et al., 2005; Moro et al., 2011; Vocat et al., 2010) and the

30

31 lateral premotor cortex (Berti et al., 2005; Fotopoulou et al., 2010; Kortte et al., 2015; Moro et al.,

32

33 2011; Vocat et al., 2010) in AHP. Nevertheless, contrary to earlier claims, AHP does not seem to be

34

35 associated with isolated lesions in the insula (Karnath et al., 2005). Instead, our results confirm the

36

37 involvement of both of these regions (see also Berti et al., 2005; Kortte et al., 2015) and

38

39 furthermore, point to a wider network of areas including perisylvian areas of the frontal, temporal

40 and parietal cortices (Heschl gyrus, rolandic operculum and anterior temporal superior gyrus) and

41

42 the underlying white matter, as well as subcortical involvement of the basal ganglia (see below).

43

44 These results are thus consistent with other, recent studies finding similar involvement of cortical

45

46 and subcortical areas and tracts in smaller samples (Besharati et al., 2014; 2016; Fotopoulou et al.,

47

48 2010; Moro et al., 2011; Romano, Gandola, Bottini, & Maravita, 2014; Vocat et al., 2010).

49

50 -------------------------------------------------------

51

52 Table 4 near here

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54 -------------------------------------------------------

55

56 Functionally, this wider pattern of lesions suggests that AHP is not the result of a pure

57

58 deficit of sensorimotor monitoring (Berti et al., 2005), or multisensory body representation

theories of AHP that propose the syndrome is caused by a collection of heterogeneous

1

2 disturbances (Davies et al., 2005; Marcel et al., 2004; Mograbi & Morris, 2013; Vuilleumier, 2004).

3

4 For example, our anosognosic patients were more impaired than hemiplegic control patients both

5

6 in neglect and executive functions. This is in line with previous reports that indicate a role of

7

8 visuospatial neglect and spatiotemporal disorientation in determining AHP in the sub-acute phase

9 (Vocat et al., 2010). Nevertheless, we did not find any correlations between severity of AHP and

10

11 these symptoms. In addition, the lesion analysis of the neuroanatomical correlates of spatial

12

13 neglect in the AHP group (see Supplementary Materials) indicates that this is selectively associated

14

15 with temporo-parieto-occipital areas. These lesions are more cortical and posterior compared to

16

17 those involved in AHP. Thus, a causative role of these symptoms in the syndrome appears unlikely,

18

19 but future studies should study their combination (see also below), as well as explore their

20

21 combined effects with other deficits, such as proprioception that we did not have the chance to

22

23 explore in this study.

24

25 Alternatively, our findings could be interpreted as the result of a functional disconnection

26

27 between top-down, premorbidly learned predictions regarding one’s body and the processing of

28

29 bottom-up ‘prediction errors’ regarding its current state (Fotopoulou, 2012, 2014, 2015). These

30

31 disconnections may occur at different levels of the neurocognitive hierarchy. For example, the

32

33 observed damage to the premotor cortex, as well as the ventral part of the superior longitudinal

34

35 fasciculus may have resulted in a disconnection between somatosensory areas in the parietal

36

37 cortex and ventral premotor and the prefrontal regions, resulting in impaired ability to detect and

38

39 monitor incongruent sensorimotor feedback (Enriquez-Geppert, Huster, Figge, & Herrmann,

40 2014), as previous studies have suggested (Berti et al., 2005; Kortte et al., 2015). Similar inabilities

41

42 in processing prediction errors (Magno, Foxe, Molholm, Robertson, & Garavan, 2006; Taylor,

43

44 Stern, & Gehring, 2007) in the domain of multisensory integration may have influenced the

45

46 behavior of patients with damage to the insula (Karnath et al., 2005). Unfortunately, there are

47

48 currently only a handful of mostly small sample studies that have included direct comparisons

49

50 between lesion and experimental results in AHP. Although mostly underpowered, the results of

51

52 such studies indeed suggest that the different behavioural variants of AHP are associated with

53

54 distinct lesion patterns (Besharati et al., 2015; Fotopoulou et al., 2010; Valentina Moro et al.,

55

56 2011). Unfortunately, unlike the present study, such studies cannot control for the precise

57

58 influence of other factors such as neglect, time from onset and the presence of DSO.

In addition, in the present study, although we did not find specific lesions associated with

1

2 AHP in the right temporo-parietal junction, we found that the anterior temporal superior gyrus is

3

4 damaged selectively in AHP as compared to the HP controls. This area has been linked previously

5

6 with deficits of perspective-taking and mentalisation in AHP (Besharati et al., 2015), potentially

7

8 explaining why patients cannot update their anosognosic beliefs based on third-person feedback

9 (Fotopoulou, 2015; Moro et al., 2011). Furthermore, the involvement of the arcuate fasciculus and

10

11 the superior longitudinal fasciculus (SLF III) in AHP, suggests a further possibility of functional

12

13 disconnection between temporo-parietal and premotor areas. In order to investigate such

14

15 hypotheses and possibilities, future large-sample studies will need to correlate lesion patterns

16

17 with findings from several well-controlled behavioral experiments tested on the same sample.

18

19

20

21 *4.2. Lesion Patterns Associated with Chronic Anosognosia*

22

23 In our study, exploratory analyses of the differences between patients who showed anosognosia

24

25 in both the sub-acute and chronic stages (>40 days), with those who recovered awareness within

26

27 40 days, revealed that AHP in acute stage is more correlated to lesions involving the insula,

28

29 caudate, putamen, internal and external capsule and the inferior occipito-frontal fasciculus. By

30

31 contrast, patients who remain unaware show more lesions in the ventral premotor cortex,

32

33 thalamus, Heschl, temporal superior cortex, the cortico-spinal tract, the arcuate anterior segment

34

35 and the corpus callosum. Lesions common to both groups were in the insula, external and internal

36

37 capsule and superior corona radiate. Thus, our findings are in line with and extend previous

38

39 findings from the only existing study to investigate the evolution of AHP over time (Vocat et al.,

40 2010), showing that chronic AHP is correlated with greater cortical damage compared with short-

41

42 lasting AHP.

43

44

45

46 *4.3. Lesion Patterns Associated with Disturbances of Body Ownership*

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48 Disturbances of body ownership (DSO) have been found to co-occur frequently with AHP (for a

49

50 review see Vallar & Ronchi, 2009). Initial studies suggested common critical lesions in the insular

51

52 cortex underlying disorders of limb ownership and action awareness (Baier & Karnath, 2008);

53

54 however, more recent investigations argued in favor of behavioural and neural dissociations

55

56 between AHP and DSO (Gandola et al., 2012; Invernizzi et al., 2013; Vallar & Ronchi, 2009). DSO

57

58 was found to be associated with more grey subcortical structures and white matter bundles, while

2011). Our study involved a number of critical direct and indirect (i.e. in relation to the HP control

1

2 group) comparisons between AHP and DSO. Although direct comparisons seemed underpowered

3

4 to detect any differences between these groups, exploratory analyses with less conservative

5

6 thresholds, as well as qualitative comparisons between pure and mixed groups against the

7

8 hemiplegic controls, revealed that DSO is associated with less cortical damage, particularly in the

9 insular cortex and rolandic operculum compared with AHP. Conversely, the damage appears more

10

11 evident in the basal ganglia and in the surrounding white matter. Taken together our results

12

13 suggest that the presence of DSO in either pure cases or concomitantly with AHP is associated

14

15 with lesion patterns that are more medial and subcortical than those associated with pure AHP. In

16

17 particular the lesion of thalamus and fornix, although not statistically significant, may suggest a

18

19 role of memory and learning in DSO symptoms.

20

21 These findings thus contradict the results of studies proposing a cortical system of

22

23 multimodal areas (including insula, lateral premotor cortex, the inferior parietal lobe and the right

24

25 posterior temporal cortex; Baier & Karnath, 2008; Ehrsson, Spence, & Passingham, 2004; Feinberg,

26

27 Haber, & Leeds, 1990; Feinberg et al., 2010; Tsakiris et al., 2007; Vallar & Ronchi, 2009) as the

28

29 main neural locus of the sense of body ownership. Instead, in agreement with more recent lesion

30

31 studies on DSO (Gandola et al., 2012; Invernizzi et al., 2013; Romano et al., 2014), our results

32

33 suggest that subcortical grey areas and related white matter tracks may be necessary for

34

35 rudimentary feelings of limb ownership, which are then presumably re-represented at the above

36

37 higher cortical areas to integrate them with other aspects of self-awareness, such as self-other

38

39 distinction, spatial and temporal self-awareness, as well as the sense of action awareness and

40 agency (Blanke, 2012; Tsakiris, Longo, & Haggard, 2010).

41

42

43

44 *4.4. Limitations*

45

46 Our study is subject to common limitations of current voxel-based, lesion analyses methods in

47

48 stroke research (Geva, Baron, Jones, Price, & Warburton, 2012; Rorden et al., 2007; Volle, Gonen-

49

50 Yaacovi, de Lacy Costello, Gilbert, & Burgess, 2011), including suboptimal characterization of

51

52 dynamic brain processes following stroke (e.g., diaschisis). Moreover, although we did examine

53

54 lesions to white matter tracts on the basis of clinical scans, specific white matter investigation

55

56 techniques, such as tractography, may offer a significant improvement to our conclusions. It

57

58 should be noted that our lesion analyses were based on dichotomous data (binomial comparison s

nuisance covariates in the statistical software (e.g. time since symptom onset). Although we were

1

2 able to overcome limitations of the Bonferroni and FDR corrections by means of the permutation

3

4 tests (Kimberg et al., 2007), the use of this statistical model in the software further limits the use

5

6 of covariates. Similar considerations apply to our exploratory lesion comparison between acute

7

8 only vs. chronic cases (dichotomous data depended on a cut-off), in which the difference between

9 scanning time and assessment time was not controlled for.

10

11 Furthermore, although we combined previous data to form a large sample that would

12

13 allow better localisation of function in AHP and related pathologies, the characteristics of the

14

15 scans used in the study differed depending on the centre they were collected. Similarly, there

16

17 were also a limited number of behavioural assessments that all three centers have used to test the

18

19 variables of interest, and future studies could provide further neuropsychological, as well as

20

21 experimental, characterization of the symptoms under consideration. Finally, the number of

22

23 patients in each subgroup were not equal, rendering some of our behavioural and lesion analyses

24

25 merely exploratory.

26

27

28

29 *4.5. Conclusions*

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31 We believe that our results, taken together, are consistent with a number of conclusions

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33 generated in previous research with smaller samples and, importantly, they are able to

34

35 disentangle some of the ambiguities generated by such smaller studies. In brief, they suggest that

36

37 anosognosia for hemiplegia does not seem to be associated only with isolated lesions to the insula

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39 and the lateral premotor cortex, but rather to a wider network of areas including perisylvian areas

40 of the frontal, temporal and parietal cortices (Heschl gyrus, rolandic operculum and anterior

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42 temporal superior gyrus) and the underlying white matter, as well as subcortical involvement of

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44 the basal ganglia. More extensive cortical damage seems to lead to more chronic anosognosia,

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46 while the subcortical involvement appears to be mostly associated with concomitant disturbances

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48 in body ownership.

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41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

**References**

1

2 Appollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., … Nichelli, P. (2005). The

3

4 Frontal Assessment Battery (FAB): normative values in an Italian population sample.

5

6

7 *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian*

8

9 *Society of Clinical Neurophysiology*, *26*(2), 108–116. <http://doi.org/10.1007/s10072-005->

10

11

12 0443-4

13

14

15 Babinski, J. (1914). Contribution to the study of mental disorders in organic cerebral hemiplegia

16

17 (anosognosia). *Rev Neurol (Paris)*, *27*, 845–848.

18

19

20 Baier, B., & Karnath, H.-O. (2008). Tight link between our sense of limb ownership and self-

21

22 awareness of actions. *Stroke*, *39*(2), 486–488.

23

24

25 Berti, A., Bottini, G., Gandola, M., Pia, L., Smania, N., Stracciari, A., … Paulesu, E. (2005). Shared

26

27

28 Cortical Anatomy for Motor Awareness and Motor Control. *Science*, *309*(5733), 488–491.

29

30 <http://doi.org/10.1126/science.1110625>

31

32

33 Berti, A., Làdavas, E., & Della Corte, M. (1996). Anosognosia for hemiplegia, neglect dyslexia, and

34

35 drawing neglect: clinical findings and theoretical considerations. *Journal of the*

36

37

38 *International Neuropsychological Society: JINS*, *2*(5), 426–440.

39

40 Besharati, S., Kopelman, M., Avesani, R., Moro, V., & Fotopoulou, A. (2015). Another perspective

41

42

43 on anosognosia: Self-observation in video replay improves motor awareness.

44

45

46 *Neuropsychological Rehabilitation*, *25*(3), 319–352.

47

48 Bisiach, E., Vallar, G., Perani, D., Papagno, C., & Berti, A. (1986). Unawareness of disease following

49

50

51 lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for

52

53 hemianopia. *Neuropsychologia*, *24*(4), 471–482.

54

55

56 Blanke, O., (2012). Multisensory brain mechanisms of bodily self-consciousness. *Nature Reviews*

57

58

59 *Neuroscience, 12*, 556-571.

Catani, M., & Thiebaut de Schotten, M. (2012). *Atlas of human brain connections*. Oxford: Oxford

1

2 University Press.

3

4

5 Cocchini G., Beschin N., Della Sala S. (2002) Chronic anosognosia: a case report and theoretical

6

7

8 account. *Neuropsychologia*, 40, 2030-2038.

9

10

11 Cocchini, G., Beschin, N., Cameron, A., Fotopoulou, A., & Della Sala, S. (2009). Anosognosia for

12

13

14 motor impairment following left brain damage. *Neuropsychology*, *23*(2), 223.

15

16 Cocchini, G., Beschin, N., Fotopoulou, A., & Della Sala, S. (2010). Explicit and implicit anosognosia

17

18

19 or upper limb motor impairment. *Neuropsychologia*, *48*(5), 1489–1494.

20

21 Cocchini G. & Della Sala S.,(2010) Assessing Anosognosia for motor and language impairments. In :

22

23

24 Prigatano, G. P. (2010). *The study of anosognosia*. Oxford University Press

25

26

27 Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. Retrieved

28

29

30 from <http://psycnet.apa.org/psycinfo/2009-00363-005>

31

32

33 Davies, M., Davies, A. A., & Coltheart, M. (2005). Anosognosia and the Two-factor Theory of

34

35 Delusions. *Mind & Language*, *20*(2), 209–236.

36

37

38 Ehrsson, H. H., Spence, C., & Passingham, R. E. (2004). That’s my hand! Activity in premotor cortex

39

40 reflects feeling of ownership of a limb. *Science*, *305*(5685), 875–877.

41

42

43 Enriquez-Geppert, S., Huster, R. J., Figge, C., & Herrmann, C. S. (2014). Self-regulation of frontal-

44

45 midline theta facilitates memory updating and mental set shifting. *Frontiers in Behavioral*

46

47

48 *Neuroscience*, *8*. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4257088/>

49

50

51 Feinberg, T. E., Haber, L. D., & Leeds, N. E. (1990). Verbal asomatognosia. *Neurology*, *40*(9), 1391–

52

53 1391.

54

55

56 Feinberg, T. E., Venneri, A., Simone, A. M., Fan, Y., & Northoff, G. (2010). The neuroanatomy of

57

58 asomatognosia and somatoparaphrenia. *Journal of Neurology, Neurosurgery, and*

59

Fletcher, P., & Fotopoulou, A. (2015). Sense of agency and its disruption: Clinical and

1

2 computational perspectives. In P. Haggard & B. Eitam (eds.) , The sense of agency (pp. 347-

3

4

5 370). New York: Oxford University Press.

6

7

8 Fo rkel, S. J., Th ieb aut d e Sch o t ten , M ., Ka wad ler , J. M ., Dell’Acqu a, F., D anek, A., & Cat an i, M .

9

10 (2014). The anatomy of fronto-occipital connections from early blunt dissections to

11

12

13 contemporary tractography. *Cortex*, 56, 73– 84.

14

15 <http://doi.org/10.1016/j.cortex.2012.09.005>

16

17

18 Fotopoulou, A. (2014). Time to get rid of the “Modular”in neuropsychology: A unified theory of

19

20 anosognosia as aberrant predictive coding. *Journal of Neuropsychology*, *8*(1), 1–19.

21

22

23 Fotopoulou, A. (2015). The virtual bodily self: Mentalisation of the body as revealed in

24

25

26 anosognosia for hemiplegia. *Consciousness and Cognition*, *33*, 500–510.

27

28 Fotopoulou, A., Jenkinson, P. M., Tsakiris, M., Haggard, P., Rudd, A., & Kopelman, M. D. (2011).

29

30

31 Mirror-view reverses somatoparaphrenia: dissociation between first-and third-person

32

33 perspectives on body ownership. *Neuropsychologia*, *49*(14), 3946–3955.

34

35

36 Fotopoulou, A. K. (2012). Illusions and delusions in anosognosia for hemiplegia: from motor

37

38

39 predictions to prior beliefs. *Brain*, *135*(5), 1344–1346.

40

41 Fotopoulou, A., Pernigo, S., Maeda, R., Rudd, A., & Kopelman, M. A. (2010). Implicit awareness in

42

43

44 anosognosia for hemiplegia: unconscious interference without conscious re-

45

46 representation. *Brain*, *133*(12), 3564–3577. <http://doi.org/10.1093/brain/awq233>

47

48

49 Fotopoulou, A., Tsakiris, M., Haggard, P., Vagopoulou, A., Rudd, A., & Kopelman, M. (2008). The

50

51 role of motor intention in motor awareness: an experimental study on anosognosia for

52

53

54 hemiplegia. *Brain*, *131*(12), 3432–3442.

55

56

57

58

59

Gandola, M., Bottini, G., Zapparoli, L., Invernizzi, P., Verardi, M., Sterzi, R., … Paulesu, E. (2014).

1

2 The physiology of motor delusions in anosognosia for hemiplegia: Implications for current

3

4

5 models of motor awareness. *Consciousness and Cognition*, *24*, 98–112.

6

7

8 Gandola, M., Invernizzi, P., Sedda, A., Ferrè, E. R., Sterzi, R., Sberna, M., … Bottini, G. (2012). An

9

10 anatomical account of somatoparaphrenia. *Cortex*, *48*(9), 1165–1178.

11

12

13 Geva, S., Baron, J.-C., Jones, P. S., Price, C. J., & Warburton, E. A. (2012). A comparison of VLSM

14

15 and VBM in a cohort of patients with post-stroke aphasia. *NeuroImage: Clinical*, *1*(1), 37–

16

17

18 47.

19

20 Gialanella, B., & Mattioli, F. (1992). Anosognosia and extrapersonal neglect as predictors of

21

22

23 functional recovery following right hemisphere stroke. *Neuropsychological Rehabilitation*,

24

25

26 *2*(3), 169–178.

27

28 Hartman-Maeir, A., Soroker, N., & Katz, N. (2001). Anosognosia for hemiplegia in stroke

29

30

31 rehabilitation. *Neurorehabilitation and Neural Repair*, *15*(3), 213–222.

32

33 Invernizzi, P., Gandola, M., Romano, D., Zapparoli, L., Bottini, G., & Paulesu, E. (2013). What is

34

35

36 mine? Behavioral and anatomical dissociations between somatoparaphrenia and

37

38

39 anosognosia for hemiplegia. *Behavioural Neurology*, *26*(1-2), 139–150.

40

41 Jackson, J. H. (1998). *Evolution and dissolution of the nervous system*. Thoemmes Press.

42

43

44 Jehkonen, M., Laihosalo, M., & Kettunen, J. (2006). Anosognosia after stroke: assessment,

45

46 occurrence, subtypes and impact on functional outcome reviewed. *Acta Neurologica*

47

48

49 *Scandinavica*, *114*(5), 293–306.

50

51 Jenkinson, P. M., Edelstyn, N. M., Drakeford, J. L., & Ellis, S. J. (2009). Reality monitoring in

52

53

54 anosognosia for hemiplegia. *Consciousness and Cognition*, *18*(2), 458–470.

55

56

57 Jenkinson, P. M., Edelstyn, N. M., & Ellis, S. J. (2009). Imagining the impossible: motor

58

59 representations in anosognosia for hemiplegia. *Neuropsychologia*, *47*(2), 481–488.

Jenkinson, P. M., & Fotopoulou, A. (2014). Understanding Babinski’s anosognosia: 100 years later.

1

2 *Cortex*, *61*, 1–4.

3

4

5 Jenkinson, P. M., Haggard, P., Ferreira, N. C., & Fotopoulou, A. (2013). Body ownership and

6

7

8 attention in the mirror: Insights from somatoparaphrenia and the rubber hand illusion.

9

10 *Neuropsychologia*, *51*(8), 1453–1462.

11

12

13 Jenkinson, P. M., Preston, C., & Ellis, S. J. (2011). Unawareness after stroke: a review and practical

14

15 guide to understanding, assessing, and managing anosognosia for hemiplegia. *Journal of*

16

17

18 *Clinical and Experimental Neuropsychology*, *33*(10), 1079–1093.

19

20 <http://doi.org/10.1080/13803395.2011.596822>

21

22

23 Karnath, H.-O., Baier, B., & Nägele, T. (2005). Awareness of the Functioning of One’s Own Limbs

24

25

26 Mediated by the Insular Cortex? *The Journal of Neuroscience*, *25*(31), 7134–7138.

27

28 <http://doi.org/10.1523/JNEUROSCI.1590-05.2005>

29

30

31 Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in Voxel-based lesion-symptom

32

33 mapping. *Journal of Cognitive Neuroscience*, *19*(7), 1067–1080.

34

35

36 <http://doi.org/10.1162/jocn.2007.19.7.1067>

37

38

39 Kortte, K. B., McWhorter, J. W., Pawlak, M. A., Slentz, J., Sur, S., & Hillis, A. E. (2015). Anosognosia

40

41 for hemiplegia: The contributory role of right inferior frontal gyrus. *Neuropsychology*,

42

43

44 *29*(3), 421.

45

46 Magno, E., Foxe, J. J., Molholm, S., Robertson, I. H., & Garavan, H. (2006). The anterior cingulate

47

48

49 and error avoidance. *The Journal of Neuroscience*, *26*(18), 4769–4773.

50

51 Marcel, A. J., Tegnér, R., & Nimmo-Smith, I. (2004). Anosognosia for plegia: Specificity, extension,

52

53

54 partiality and disunity of bodily unawareness. *Cortex*, *40*(1), 19–40.

55

56

57 Martino, J., De Witt Hamer, P. C., Berger, M. S., Lawton, M. T., Arnold, C. M., de Lucas, E. M., &

58

59 Duffau, H. (2013). Analysis of the subcomponents and cortical terminations of the

perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study.

1

2 *Brain Structure & Function*, *218*(1), 105–121. <http://doi.org/10.1007/s00429-012-0386-5>

3

4

5 McIntosh, R. D., Brodie, E. E., Beschin, N., & Robertson, I. H. (2000). Improving the clinical

6

7

8 diagnosis of personal neglect: a reformulated comb and razor test. *Cortex; a Journal*

9

10 *Devoted to the Study of the Nervous System and Behavior*, *36*(2), 289–292.

11

12

13 Medina, J., Kimberg, D. Y., Chatterjee, A., & Coslett, H. B. (2010). Inappropriate usage of the

14

15 Brunner-Munzel test in recent voxel-based lesion-symptom mapping studies.

16

17

18 *Neuropsychologia*, *48*(1), 341–343. <http://doi.org/10.1016/j.neuropsychologia.2009.09.016>

19

20 Mograbi, D. C., & Morris, R. G. (2013). Implicit awareness in anosognosia: Clinical observations,

21

22

23 experimental evidence, and theoretical implications. *Cognitive Neuroscience*, *4*(3-4), 181–

24

25

26 197.

27

28 Mori, S., Wakana, S., Zijl, P. C. M. van, & Nagae-Poetscher, L. M. (2005). *MRI Atlas of Human White*

29

30

31 *Matter*. Elsevier.

32

33 Moro, V., Pernigo, S., Zapparoli, P., & Cordioli, Z. (2011). Phenomenology and neural correlates of

34

35

36 implicit and emergent motor awareness in patients with anosognosia for hemiplegia.

37

38

39 *Behavioural Brain …*. Retrieved from

40

41 <http://www.sciencedirect.com/science/article/pii/S0166432811005250>

42

43

44 Moro, V., Pernigo, S., Zapparoli, P., Cordioli, Z., & Aglioti, S. M. (2011). Phenomenology and neural

45

46 correlates of implicit and emergent motor awareness in patients with anosognosia for

47

48

49 hemiplegia. *Behavioural Brain Research*, *225*(1), 259–269.

50

51 Naidich, T. P., Kang, E., Fatterpekar, G. M., Delman, B. N., Gultekin, S. H., Wolfe, D., … Yousry, T. A.

52

53

54 (2004). The Insula: Anatomic Study and MR Imaging Display at 1.5 T. *American Journal of*

55

56

57 *Neuroradiology*, 25(2), 222– 232.

58

Nurmi L.M.E., Jehkonen M. (2014) Assessing anosognosias after stroke: a review of the methods

1

2 used and developed over the past 35 years. Cortex, 61: 43-63.

3

4

5

6 Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory.

7

8

9 *Neuropsychologia*, *9*(1), 97–113.

10

11 Orfei, M. D., Robinson, R. G., Prigatano, G. P., Starkstein, S., Rüsch, N., Bria, P., … Spalletta, G.

12

13

14 (2007). Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a

15

16

17 systematic review of the literature. *Brain*, *130*(12), 3075–3090.

18

19 Pernigo, S., Moro, V., Avesani, R., Miatello, C., Urgesi, C., & Aglioti, S. M. (2012). Massive somatic

20

21

22 deafferentation and motor deefferentation of the lower part of the body impair its visual

23

24 recognition: a psychophysical study of patients with spinal cord injury. *The European*

25

26

27 *Journal of Neuroscience*[. http://doi.org/10.1111/j.1460-9568.2012.08266.x](http://doi.org/10.1111/j.1460-9568.2012.08266.x)

28

29 Phipps, M. C. (2003). Inequalities Between Hypergeometric Tails. *Journal of Applied Mathematics*

30

31

32 *and Decision Sciences*, *7*(3), 165–174. <http://doi.org/10.1207/S15327612JAMD0703_03>

33

34

35 Pia, L., Neppi-Modona, M., Ricci, R., & Berti, A. (2004). The anatomy of anosognosia for

36

37 hemiplegia: a meta-analysis. *Cortex*, *40*(2), 367–377.

38

39

40 Prigatano, G. P. (2010). *The study of anosognosia*. Oxford University Press. Retrieved from

41

42 https://books.google.it/books?hl=it&lr=&id=d4S-

43

44

45 T0NboMQC&oi=fnd&pg=PR9&dq=prigatano+anosognosia&ots=Pf586qlAJK&sig=tXDaFSO8

46

47

48 WtFTgyLkczcQROBtF7c

49

50 Ramachandran, V. S., & Rogers-Ramachandran, D. (2000). Phantom limbs and neural plasticity.

51

52

53 *Archives of Neurology*, *57*(3), 317–320.

54

55 Romano, D., Gandola, M., Bottini, G., & Maravita, A. (2014). Arousal responses to noxious stimuli

56

57

58 in somatoparaphrenia and anosognosia: clues to body awareness. *Brain*, awu009.

Rorden, C., Fridriksson, J., & Karnath, H.-O. (2009). An evaluation of traditional and novel tools for

1

2 lesion behavior mapping. *NeuroImage*, *44*(4), 1355–1362.

3

4

5 <http://doi.org/10.1016/j.neuroimage.2008.09.031>

6

7

8 Rorden, C., & Karnath, H.-O. (2004). Using human brain lesions to infer function: a relic from a past

9

10 era in the fMRI age? *Nature Reviews Neuroscience*, *5*(10), 812–819.

11

12

13 <http://doi.org/10.1038/nrn1521>

14

15 Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of*

16

17

18 *Cognitive Neuroscience*, *19*(7), 1081–1088. <http://doi.org/10.1162/jocn.2007.19.7.1081>

19

20 Scandola, M., Tidoni, E., Avesani, R., Brunelli, G., Aglioti, S. M., & Moro, V. (2014). Rubber hand

21

22

23 illusion induced by touching the face ipsilaterally to a deprived hand: evidence for plastic

24

25

26 “somatotopic” remapping in tetraplegics. *Frontiers in Human Neuroscience*, *8*. Retrieved

27

28 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4050649/>

29

30

31 Schmahmann, J. D., & Pandya, D. N. (2007). The complex history of the fronto-occipital fasciculus.

32

33 *Journal of the History of the Neurosciences*, 16(4), 362– 377.

34

35

36 Spalletta, G., Serra, L., Fadda, L., Ripa, A., Bria, P., Caltagirone C. (2007). Unawareness of motor

37

38

39 impariment and emotions in right hemispheric stroke: a preliminary investigation.

40

41 *International Journal of Geriatric Psychiatry,* 22, 1241-1246.

42

43

44

45 Taylor, S. F., Stern, E. R., & Gehring, W. J. (2007). Neural systems for error monitoring recent

46

47 findings and theoretical perspectives. *The Neuroscientist*, *13*(2), 160–172.

48

49

50

51 Thiebaut de Schotten, M., Ffytche, D. H., Bizzi, A., Dell’Acqua, F., Allin, M., Walshe, M., … Catani,

52

53 M. (2011). Atlasing location, asymmetry and inter-subject variability of white matter tracts

54

55

56 in the human brain with MR diffusion tractography. *NeuroImage*, *54*(1), 49–59.

57

58 <http://doi.org/10.1016/j.neuroimage.2010.07.055>

59

Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., & Fink, G. R. (2007). Neural signatures of body

1

2 ownership: a sensory network for bodily self-consciousness. *Cerebral Cortex*, *17*(10), 2235–

3

4

5 2244.

6

7

8 Tsakiris, M., Longo, M. R., & Haggard, P. (2010). Having a body versus moving your body: neural

9

10 signatures of agency and body-ownership. *Neuropsychologia*, *48*(9), 2740–2749.

11

12

13 <http://doi.org/10.1016/j.neuropsychologia.2010.05.021>

14

15 Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot,

16

17

18 M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic

19

20 anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, *15*(1), 273–289.

21

22

23 <http://doi.org/10.1006/nimg.2001.0978>

24

25

26 Vallar, G., & Ronchi, R. (2009). Somatoparaphrenia: a body delusion. A review of the

27

28 neuropsychological literature. *Experimental Brain Research*, *192*(3), 533–551.

29

30

31 Vocat, R., Staub, F., Stroppini, T., & Vuilleumier, P. (2010). Anosognosia for hemiplegia: a clinical-

32

33 anatomical prospective study. *Brain*, *133*(12), 3578–3597.

34

35

36 Volle, E., Gonen-Yaacovi, G., de Lacy Costello, A., Gilbert, S. J., & Burgess, P. W. (2011). The role of

37

38

39 rostral prefrontal cortex in prospective memory: A voxel-based lesion study.

40

41 *Neuropsychologia*, *49*(8), 2185–2198.

42

43

44 Vuilleumier, P. (2004). Anosognosia: the neurology of beliefs and uncertainties. *Cortex*, *40*(1), 9–

45

46 17.

47

48

49 Wechsler, D. (1997). Wechsler Adult Intelligence Scale® - Third Edition (WAIS®-III). *San Antonio, TX:*

50

51 *The Psychological Corporation*.

52

53

54 Wilson, B., Cockburn, J., & Halligan, P. (1987). Development of a behavioral test of visuospatial

55

56

57 neglect. *Archives of Physical Medicine and Rehabilitation*, *68*(2), 98–102.

Zeller, D., Gross, C., Bartsch, A., Johansen-Berg, H., & Classen, J. (2011). Ventral premotor cortex

1

2 may be required for dynamic changes in the feeling of limb ownership: a lesion study. *The*

3

4

5 *Journal of Neuroscience*, *31*(13), 4852–4857.

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

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**Captions to Tables and Figures**

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4 **Table 1.** Demographic variables and scores on the neuropsychological tasks. For each

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6 experimental group, mean scores (± standard deviation) of demographic variables and medians (±

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8 interquartile range) of neuropsychological measures are reported.

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10

11 **Table 2.** Significant voxels resulting from the comparison of lesions of all AHP patients (first

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13 column), patients who recovered awareness within 40 days from onset (central column), and

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15 patients who did not recover awareness within 40 days of onset (column on the right), compared

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17 to the HP controls. The amount of voxels for each region indicated in the brain atlas of gray (AAL)

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19 and white matter (JHU) are reported.

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23 **Table 3.** Number of significant voxels (atlas of gray matter – AAL - and white matter –JHU - and

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25 NatBrainLab’s atlas) resulting from the comparison of the lesions of AHP+DSO (first column) and

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27 AHP+DSO plus DSO patients (second column) compared to HP (indirect comparisons: *p*<0.05,

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29 5000 permutation). The results of the direct comparison between AHP+DSO versus AHP and vice

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31 versa are shown in the two columns on the right of the table (*p*<0.01, FDR correction). In each

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33 column the numbers indicate the regions significantly more lesioned in the first with respect to

34

35 the second group.

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37

38

39 **Table 3.** Number of significant voxels (atlas of gray matter – AAL - and white matter –JHU - and

40 NatBrainLab’s atlas) resulting from the comparison of the lesions of AHP+DSO (first column) and

41

42 AHP+DSO plus DSO patients (second column) compared to HP (indirect comparisons: *p*<0.05,

43

44 5000 permutation). The results of the direct comparison between AHP+DSO versus AHP and vice

45

46 versa are shown in the two columns on the right of the table (*p*<0.01, FDR correction). In each

47

48 column the numbers indicate the regions significantly more lesioned in the first with respect to

49

50 the second group.

51

52

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54 **Table 4.** The results of previous studies of lesional analysis in AHP are reported. In this review,

55

56 patients suffering from crossed anosognosia are excluded. In addition, the single case study,

patients' lesions were not compared with controls. In Italic previous studies involving some of the

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2 patients of this study sample.

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8 **Figure 1.** Lesions associated with ‘pure’ AHP patients as compared to HP patients. A = The areas

9 significantly associated with AHP in the AHP vs. HP comparison. The numbers above the brain

10

11 slices indicates the corresponding MNI axial coordinates. L = left; R = Right; B = Heat map of the

12

13 voxels with power enough to detect a significant results. Different colors represent area under

14

15 ROC curve (AUROC) scores, ranging between 0.5 (minimum power) to 1 (maximum discrimination

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17 power); C = Sagittal cut in which three cortical clusters in the subcentral gyrus and around the

18

19 insula are indicated by dark blue circles. These touch the Rolandic operculum (ventral premotor

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21 cortex) (1), the Insula (2), the Heschl and superior temporal gyri (3); D = Side view of the clusters of

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23 lesions overimposed on a 3D reproduction of the JHU atlas.; E = DTI tractography reconstruction of

24

25 the anterior segment of the SLF (1) and the arcuate fasciculus (3) (figure from Martino et al.,2013).

26

27 The same tracts are depicted in light blue and in green in the JHU atlas (panel D) and Natbrainlab

28

29 atlas (panel F), respectively; F = Rear, side and front views of the clusters of lesions overimposed

30

31 on a 3D reproduction of the Natbrainlab atlas.

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34

35 **Figure 2.** The lesional comparison with the damage in HP patients shows the lesions significantly

36

37 associated to somatoparaphrenia in AHP+DSO and DSO patients (in dark blue). In the figure these

38

39 are shown together with lesions involved in AHP (in red). Below is represented a heat map of the

40 voxels with enough power to detect a significant result; different colors represent area under ROC

41

42 curve (AUROC) scores, ranging between 0.5 (minimum power, in green) to 1 (maximum

43

44 discrimination power, in red). Numbers above the brain slices indicate the MNI axial coordinates. L

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46 = left. R = right.

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50 **Figure 3.** The comparison between lesions significantly associated with AHP+DSO vs. isolated AHP

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52 and vice versa. A. Regions more involved in AHP+DSO than in AHP are shown. B. Lesions in

53

54 amygdala are marginally more frequent in AHP than in AHP+DSO. Numbers above the brain slices

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56 indicate the MNI axial coordinates. L = left. R = right. Below each comparison is represented a heat

under ROC curve (AUROC) scores, ranging between 0.5 (minimum power) to 1 (maximum

1

2 discrimination power).

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Figure1

[Click here to do"""'loaj high resolution image](http://ees.elsevier.com/cortex/download.aspx?id=158686&amp;guid=03b75175-13f0-462e-8a9a-a8bfa2bf8d63&amp;scheme=1)

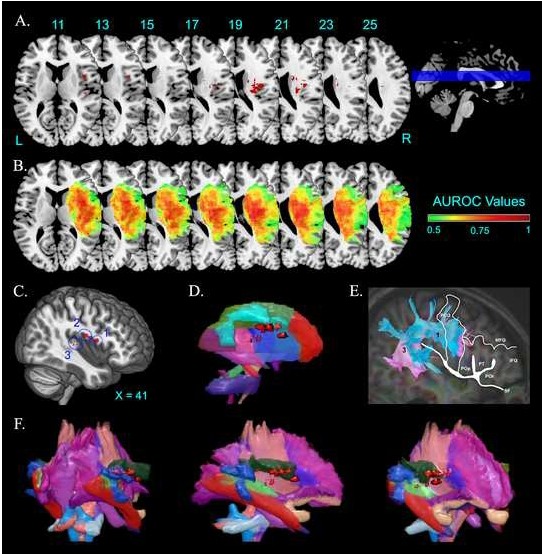


Figure2

Click here to do"""'loaj high resolution image

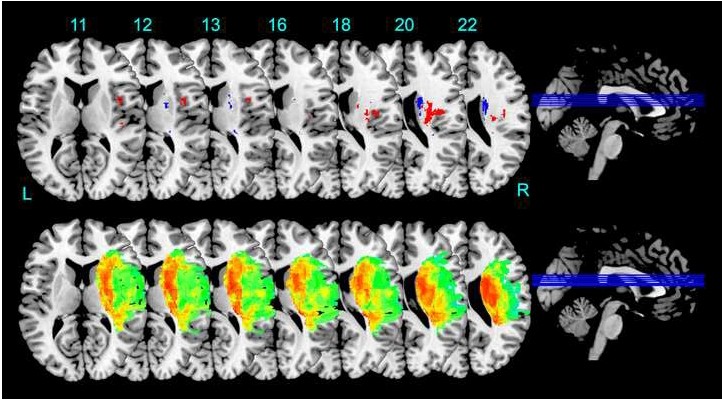
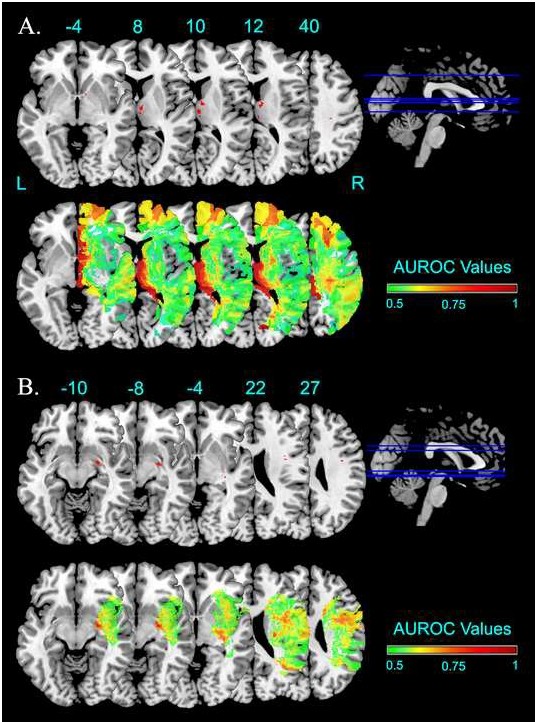


Figure3

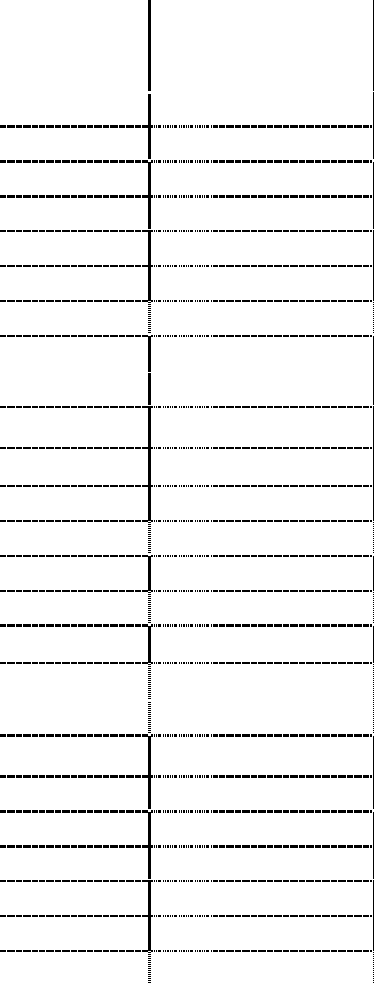
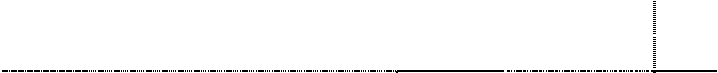
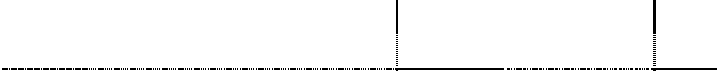
[Click here to do"""'loaj high resolution image](http://ees.elsevier.com/cortex/download.aspx?id=158689&amp;guid=2981cd57-c718-4284-8816-5d4b427682c4&amp;scheme=1)



**Table1**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Socio-demographic** | **AHP**  (N = 25) | **AHP+DSO**  (N = 13) | **HP Controls**  (N = 28) | **AHP VS HP** | **AHP+DSO VS HP** | **AHP VS**  **AHP+DSO** |
| Gender | F=12, M=13 | F=3, M=10 | F=6, M=22 | 2(1, N = 53)= 4.16, | 2(1, N = 41) = 0.01, | 2(1, N = 38) = 2.22, |
|  |  |  |  | *P =* 0.04 | *P =* 0.91 | *P =* 0.14 |
| Age | 68 ± 11 | 67 ± 13 | 64 ± 13 | t(51) = 1.32, *P =* 0.19 | t(39) =0.67, *P =* 0.51 | t(36) = 0.35, *P =* 0.72 |
| Handedness | R | R | R |  |  |  |
| **Lesion Onset Interval** |  |  |  |  |  |  |
| Test onset (days) | 34 ± 26 | 49 ± 42 | 48 ± 53 | t(51) = 1.52, *P =* 0.13 | t(39) =0.1, *P =* 0.92 | t(36) = 1.8, *P =* 0.08 |
| Chronic Ahp/Dso (>40 days) | 14/20 (70%) | 11/12 (92%) |  |  |  | 2 (1, N = 57) = 0.25, |
|  |  |  |  |  |  | *P =* 0.62 |
| **Anosognosia** |  |  |  |  |  |  |
| Bisiach (0-3) | 2 ± 1 | 3 ± 0 | 0 |  |  |  |
| Berti LUL | 1.33 ± 0.94 | 1 ± 0.75 | 0 |  |  |  |
| Berti LLL | 1.88 ± 1 | 2 ± 0.25 | 0 |  |  |  |
| Composite score (%) | 72% ± 17.6 | 89% ± 33.3 | 0% | U(51) = 101, z = 4.22, | U(39) = 21, z = 3.19, | U(36) = 109, z = 1.28, |
|  |  |  |  | *P <* 0.0001 | *P =* 0.003 | *P =* 0.4 |
| **Neglect** |  |  |  |  |  |  |
| Line Canc. (36, omissions) | 17 ± 11 | 23 ± 9 | 12 ± 8 |  |  |  |
| Star Canc. (56, omissions) | 31 ± 20 | 38 ± 11 | 13 ± 18 |  |  |  |
| Copy | 1.1 ± 1.4 | 1.4 ± 1.6 | 2.4 ± 1.3 |  |  |  |
| Composite score (%) | 65% ± 47.6 | 68% ± 25.5 | 31% ± 34.8 | U(50) = 139, z = 3.44, | U(38) = 56, z = 3.11, | U(34) = 141, z = 1.4, |
|  |  |  |  | *P =* 0.0011 | *P =* 0.0038 | *P =* 1 |
| **Personal Neglect** |  |  |  |  |  |  |
| Comb & Razor | -0.13 ± 0.5 | -0.51 ± 0.44 | -0.04 ± 0.21 | U(49) = 225, z = 1.51, | U(34) = 46, z = 2.26, | U(29) = 69, z = 0.53, |
|  |  |  |  | *P =* 0.26 | *P =* 0.048 | *P =* 1 |
| **Executive functions** |  |  |  |  |  |  |
| Similarities | 3 ± 5 | 6 ± 5 | 16 ± 6.9 | U(29) = 21.5, z = 3.72, | U(21) = 13, z = 2.65, | U(20) = 48.5, z = 0.77, |
|  |  |  |  | *P <* 0.001 | *P =* 0.016 | *P =* 1 |

**Table2**



AHP *vs* HP

*alls* (25 VS 28)

*AHPacute vs HP*

(6 VS 28)

*AHPchronic vs HP*

(14 VS 28)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | N > 0 *(x, y, z)* |  | N > 0 *(x, y, z)* |  | N > 0 *(x, y, z)* |  |

**AAL**

**JHU**

**Nat Brain Lab**

*Frontal Inf Opercularis* 3 *(39,9,11)*

*Rolandic Operculum* 164 *(38,-6,20)* 44  *(39,-10,21) Insula* 237 *(29,-16,19)* 127  *(34,26,6)* 27  *(29,-19,19) Caudate* 24 *(22,3,21)* 3  *(22,3,21)*

*Putamen* 109  *(28,9,9)*

*Thalamus* 4 *(20,-19,13) Heschl* 15 *(41,-20,6)* 17 *(43,-20,7) Temporal Sup.* 6 *(42,-24,6)* 21 *(42,-31,15) Body of corpus callosum* 2 *(17,8,29) Anterior limb of int capsule* 10 *(20,-2,18)*

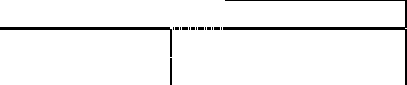
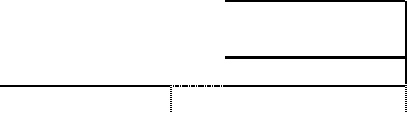
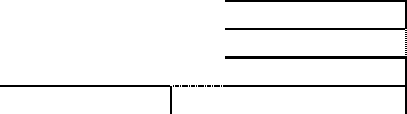
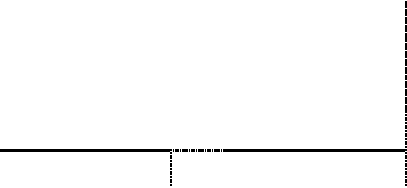
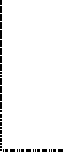
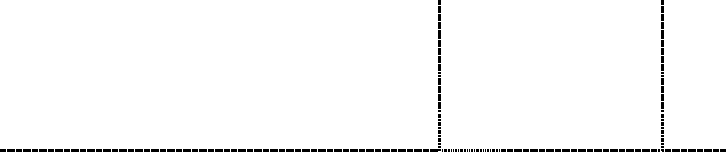
*Post. limb of internal capsule* 7  *(20,-19,13) Ant. corona radiate* 8  *(24,15,11)*

*Sup. corona radiate* 268 *(29,-16,19)* 3  *(22,3,21)* 103  *(29,-14,19)*

*Post. corona radiate* 17  *(26,-34,21) External capsule* 25 *(30,-10,18)* 50  *(28,9,9)* 5  *(32,-41,16) Sup. longitudinal fasciculus* 37 *(31,0,19)* 17 *(40,-30,-6) ~~Sup. fronto-occipital fasciculus~~* ~~34~~ *(21,0,20)*  ~~2~~ *(21,0,20)*

*Internal Capsule* 66 *(30,-12,19)* 25 *(25,13,11)*  12  *(30,-12,19) Cortico Spinal Tract*  235 *(29,-16,19)* 108  *(29,-14,19) Cortico\_Ponto\_Cerebellum*  7 *(27,-11,20)* 23  *(20,-19,13) Arcuate\_Anterior\_Segment 302 (38,-8,20)* 68 (33,-31,21) *Long\_Segment 3 (31,-15,22)* 1  *(33,-31,22) Arcuate\_Posterior\_Segment 2 (35,-45,24)* 1  *(33,-32,21) Corpus\_Callosum*  2 *(20,3,24)*  30  *(16,-1,28) Inf.\_Occipito\_Frontal\_Fasciculus* 49 (31,14,-5)

**Table3**



*Frontal Inf Opercularis Rolandic Operculum Insula*

**AHP+DSO**

*VS* **HP** (13 *VS* 28)

N > 0 *(x, y, z)*

**AHP+DSO, DSO AHP+DSO AHP** *VS* **AHP+DSO**

*VS* **HP** (17 *VS* 28) *VS* **AHP** (13 *VS* 25) (25 *VS* 13)

N > 0 *(x, y, z)* N > 0 *(x, y, z)* N > 0 *(x, y, z)*

**AAL**

*Amygdala* 16 *(25, -6, -10) Caudate* 1 *(20,11,14)* 215 *(20,2,22)* 6 *(9,1,15)*

*Pallidum* 6 *(13,5,0) Thalamus* 213  *(4,-9,8) Putamen* 15 *(21,0,12)* 16 *(23,-2,12)*

*Heschl*

*Temporal Superior*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Anterior limb of int capsule* 13 | *(20,2,12)* | 27 | *(21,1,13)* | 9 | *(13,5,1)* |  |

**JHU**

*Retrolenticular part of int capsule* 3 *(27,-30,13)* 15 *(27,-30,13)* 3 *(34,-22,-3) Superior corona radiate* 25 *(22,2,21)*

*Posterior corona radiate* 1 *(21,-29,27)*

*External capsule* 1 *(31,-19,-3)*

*Sup longitudinal fasciculus* 3 *(27,-23,40)*

*Post. thalamic radiation* 3 *(28,-45,17)*

*~~Sup fronto-occipital fasciculus~~*

168 *(21,0,19)*

**NatBrainLab**

*Internal Capsule* 6 *(26,-29,13)* 46 *(26,-29,13)* 2 *(28,-45,16) Cortico Spinal Tract* 35 *(20,2,12)* 54 *(21,-3,12)* 11 *(13,5,1) Cortico\_Ponto\_Cerebellum* 2 *(27,-30,13)* 4 *(27,-30,13)*

*Anterior\_Commissure* 2 *(9,7,-3) 24 (25,-6,-10) Arcuate Anterior\_Segment* 1 *(33,-32,20)* 2 *(33,-32,20)*

*Long Segment*

*Arcuate Posterior Segment* 3 *(33,-32,21)* 1 *(33,-32,21)*

*Corpus Callosum* 54 *(14,4,20)* 11 *(28,-45,17)*

*Inferior\_Longitudinal\_Fasciculus 17 (26,-7,-9)*

*Inferior\_Occipito\_Frontal\_Fasciculus 6 (29,-7,-9)*

*Optic radiations 3 (31,-19,-3)*

*Uncinate 4 (26,-5,-9)*

Fornix 155 *(7,1,2)*

**Table4**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | n. patient  s | n. AHP | time int. | lesion sites associated with AHP |
| Besharati et al.,  2016 | 30 | 15 | <30 d | Inf Front Gyrus; Mid Front Gyrus; Sup Temporal Gyrus |
| Piedimonte et al.,  2016 | 6 | 1 | 12 m | Mid. Sup Temporal gyrus; Post Insula |
|  |  |  |  | Periventricular temporal WM |
|  |  | 1 | 2 m | Hippocampus;Thalamus; Putamen; Ant. Post. Insula |
|  |  |  |  | Periventricular temporal WM |
| Kortte et al.,  2015 | 35 | 8 | 48h | Pars Orbitalis; Broca; Pars Trinagularis |
| Moro et al., 2015  \*\* | 4 | 4 | >72 d | Frontal Inf.; Rolandic Operc.; Insula; Hippocampus;  Parahip Cortex; |
|  |  |  |  | Amigdala; Sup. Mid. Inf Temporal; Basal Ganglia;  Int. Capsule; Corona Radiate; Sagittal Stratum; Ext  Capsule; Sup.  Longitudinal Fasc.; Sup Fronto-occipital Fasc. Uncinate  Fasciculus |
| Besharati et al.,  2014 | 15 | 8 | <7 d | Ant Post Insula Ribbon; Post Basal Ganglia; Dorsal  Pericentral Areas |
| Saj et al., 2014 | 10 | 5 | <15 d | Temporo-Parietal J.; Insula |
| Gandola et al.,  2014 | 11 | 5 | <12 d | Basal ganglia; Thalamus; Ventral Premotor; Insula |
| Vocat et al., 2013 | 9 | 4 | not  specified | Parieto-Temporal J |
|  |  |  |  | Subcortical WM |
| Pia et al., 2013 | 6 | 1 | 71 d | Ventral Premotor Cortex |
| Garbarini et al.,  2012\*\* | 10 | 1 | 62 d | Temporo-Parietal Cortex; Thalamus: Post Insula; |
|  |  | 1 | 32 d | Periventricular temporo-parietal WM  Inf. Mid. Sup Temporal G.; Angular G; Supramarginal G; Lateral Premotor; |
|  |  |  |  | Ant. Post Insula; Precentral G; Post Central G.; Thalamus,  Putamen; |
|  |  |  |  | Int. Ext Capsule; F-T-P-O WM |
|  |  | 1 | 28 d | Mid. Sup Occipital G.; Mid. Sup. Temporal G.; Angular G; |

Sup Parietal Lobe; Post Insula; Internal Capsule

Rolandic Operculum; Insula; Sup Temporal gyrus; Fusiform

*Moro et al., 2011* 24 12 22-177 d

G.;

Cingolum; Hippocampus; Caudate; Thalamus

sub-cortical WM Vocat et al., 2010 58 32% 3 d Insula; Ant Int Caps.;

Ant Periventricular WM

Insula; Ant Int Caps.; Premotor C; Dorsal Cingulate; P-T

18% 7 d

Cortex;

Hyppocampus; Amigdala

Ant Periventricular WM

*Fotopoulou et al.,*

*2010* 14 7 <40 d

Rolandic Operculum; Insula; Temporal Sup. Pole; Amigdala; Basal ganglia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Baier & Karnath  2008 | 22 | 11 (+DSO) | <10 d | Post Insula |
| Karnath et al.,  2005 | 27 | 14 | <14 d | Post Insula; Temporo-Parietal C:, Basal Ganglia; |
|  |  |  |  | Subcortical WM |
| Berti et al., 2005 | 30 | 17 | not specified | Dorsal Premotor C.; Inf. Mid. Front. G.; Somatosensory C.; |
|  |  |  |  | Primary Motor C., Insula. |

Table 4. The results of previous studies of lesional analysis in AHP are reported. In this review, patients suffering from crossed anosognosia are excluded. In addition, the single case study, where the AHP patient's lesion was

not compared with controls were not reported. \*\* = these patients' lesions were not compared with controls

In *Italic* previous studies involving some of the patients of this study sample.