Research report

Phenomenology and neural correlates of implicit and emergent motor awareness in patients with anosognosia for hemiplegia

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ABSTRACT

Anosognosia for hemiplegia (AH) is characterized by a lack of awareness of motor disorders and appears associated with fronto-temporal-parietal damage. Neuropsychological evidence indicates that behavioral indices of residual forms of motor awareness may co-exist with explicit denial of impairment. Here we explore whether the attempt by AH patients to perform an action may disclose residual forms of motor awareness and whether such forms are underpinned by different neural structures. Twelve hemiplegic patients affected by AH were tested in tasks assessing: (i) implicit awareness (IA), indexed by discrepancies between verbal reports and actual motor behavior; (ii) emergent awareness (EA), indexed by increased verbal awareness induced by the attempt to perform actions. IA and EA were found in five and three patients, respectively. Lesion analysis indicates that while the lack of IA is associated with damage to subcortical white matter anterior to the basal ganglia, lack of EA is linked to damage to cortical regions including insulo-frontal, temporal and parietal structures. Our results indicate that deficits in explicit and implicit awareness are associated with lesions involving different cortico–subcortical structures. Moreover, the results show that the attempt to perform an action may ameliorate body awareness deficits and have implications for rehabilitation.

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1. Introduction

The term anosognosia refers to the lack of awareness of neurological and neuropsychological deficits. Thus anosognosic patients do not recognize or underestimate the severity of their motor, sensory or cognitive (i.e. memory, language) impairment [30,48]. Anosognosia for hemiplegia (AH) refers to conditions where patients report being able to move a limb that is, however, paralyzed and to cases where the awareness deficit seems to selectively involve motor functions. Although AH typically occurs after right brain lesions and involves the left hemisoma, it has been demonstrated that the left brain may also play a role in the syndrome. Recent evidence supports the hypothesis that the frequency of anosognosia in left brain damaged patients is underestimated [17]. Note that in clinical practice anosognosia has not been investigated systematically in left damaged patients. This may be due to at least two reasons. The first is that assessment of anosognosia has been typically based on linguistic tests that may turn out to be challenging for left brain damaged patients in whom language deficits typically occur. The second is that anosognosia for hemiplegia has been typically associated with personal neglect that is observed mainly in right brain damaged patients.

Studies suggest that AH is a specific syndrome which cannot be explained by concomitant neurological deficits such as sensory deafferentation, presence of contralesional spatial neglect, mental confusion or deficits in frontal lobe functions [18,33,37,46]. In particular, anosognosia for sensory and motor neurological deficits is a multi-componential syndrome that may include a number of specific deficits deriving from impairment of anatomo–functionally discrete monitoring systems, each involved in the general control and monitoring of motor, sensory, spatial, memory, and language functions [39,56,63]. The finding that lesions affecting premotor areas, the cortical regions involved in motor planning and control, are also lesioned in AH [9], provides data in support of the hypothesis regarding deficits in domain-specific awareness modules [63].

Seminal studies suggest that AH may arise from the patient’s inability to form motor intentions [30]. It is considered that the intention to execute an action calls into play a forward model that generates accurate predictions about the impending sensory feedback. If an intended movement is not performed as planned, a “comparator” will detect a mismatch between the predicted and expected sensory inputs.

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actual sensory feedback [30]. If the comparator fails, subjects are unable to recognize inaccurate movements or to consider actions as having been executed, even when no movement has actually been initiated. In this hypothesis the role of action in awareness is thus largely emphasized.

Nevertheless, AH has been investigated mainly by interviewing patients about their complaints and motor deficits (e.g. “Would you like to raise your hand?” “Have you done it?”) [11, 22, 32, 58] rather than by direct behavioral observation of their action or attempt to act. Thus until now mainly verbal, declarative awareness has been investigated and information about other possible forms of awareness has been comparatively meager until very recently. Interestingly, studies have now started to address more systematically the influence of motor intentions on the phenomenology of AH [16, 26, 34].

In the present study, we investigated whether the attempt to perform everyday actions may highlight residual forms of awareness in AH. To this aim, we capitalized on two notions. The first is that in AH implicit forms of awareness may co-exist with deficits of declarative, explicit awareness [39, 51, 66]. We therefore devised a task to disclose whether the performance of the unaffected limb of AH patients was implicitly influenced by the presence of the paralyzed limb. In particular, we expected that patients who are totally unaware of their left paralysis would grasp a large, heavy object by positioning their right hand to the right of the object, as though they were performing the action bimanually. In contrast, patients showing implicit awareness would shift their right hand towards the center of the object in order to perform the task effectively.

The second notion at the basis of our study is related to models of awareness [21, 44] based on a three level hierarchy that comprises: (i) intellectual awareness, i.e. the generic ability to recognize a deficit; (ii) emergent awareness, a condition in which a patient becomes declaratively aware of his/her deficits only when pushed to perform an action with the affected body part; (iii) anticipatory awareness, i.e. the ability to anticipate a deficit before it occurs and to set up compensatory strategies. Typically, AH patients do not show anticipatory awareness. However they may exhibit a certain degree of intellectual awareness. For example, they can report that they are in hospital and participating in a rehabilitation program. We thus devised a task to distinguish anticipatory from emergent awareness in order to test whether verbal reports indexing anosognosia were influenced by the specific request to perform a given action also involving the paralytic limb. Any change in the linguistic report of one’s own motor deficits induced by the attempt to move is considered an index of emergent awareness. For example, reporting being able to drive a car, but admitting that this is not the case in relation to the attempt to actually perform the task would hint at the presence of emergent awareness.

While it has been shown that the neural structures associated with anosognosia for hemiplegia may vary according to the length of time since injury [35, 65], only one study has explored the neural substrates of implicit awareness [24]. Moreover, to the best of our knowledge, no study has investigated thus far whether implicit and emergent awareness are underpinned by different neural substrates. To this aim, using advanced brain lesion mapping procedures [5, 53], we explored whether lesions to different nodes of the network underpinning body awareness are causatively associated with lack of implicit and emergent awareness.

2. Methods

2.1. Participants

Twelve patients affected by severe hemiplegia (no movements at upper arm) and AH were recruited at the Rehabilitation Unit of the Sacro Cuore Hospital (Negrar, Verona, Italy) over a 36-month period. None of them had a history of psychiatric diseases or a previous neurological history. The anosognosia for hemiplegia was ascertained by means of a clinical examination in which subjects were asked to touch the examiner’s hand with their paralyzed hand and to state whether or not they had succeeded in performing the requested act (score 0: patient acknowledges motor deficit; 1: patient does not acknowledge motor deficit but recognizes that he/she has not touched the examiner’s hand; 2: patient denies motor deficit and the failure to touch the examiner’s hand) [10]. Patients were considered to be anosognosic when at this clinical interview their score was 1 or 2 [42, 26], corresponding (although not perfectly) to a score of 2 or 3 on the Bisiach scale [11].

The results of neuropsychological screening and the extent and site of the lesion in AH patients (AHG) were compared with the data of those subjects affected by hemiplegia but without any signs of anosognosia, either at the moment of assessment or in the acute phase of their clinical history (CG). All patients gave their informed consent to participate in the study. The procedures were approved by the local ethics committee and the body was carried out according to the principles of the Declaration of Helsinki.

The two groups were matched for age (AHG = M: 62.42 years, SD: 13.15; range: 40–78; CG = M: 66.08 years; SD: 8.62; range: 51–79, t2 = −0.81, p = 0.43), education (AHG = M: 5.92 years; SD: 1.97; range: 3–8; CG = M: 6.25 years; SD: 1.54; range: 5–8, t2 = −0.46, p = 0.65) and interval between lesion and assessment (AHG = M: 74.58 days; SD: 51.34; range: 22–177; CG = M: 94.25 days; SD: 56.71; range: 27–210, t2 = 0.89, p = 0.38). All the patients resulted right-handed in the test for handedness [14]. However, the only patient who sustained a left hemisphere lesion (patient FG, Fig. 1E) declared he was originally left-handed but had been forced in childhood to use his right hand. This patient did not show spatial distortions or parts of any language (AAT) [38] but clear signs of frontal damage. Lesion site and size in AHG and CG patients were documented by means of CT (see Fig. 1 and Table S1). Additional demographical and clinical data concerning the two patient groups are shown in Table 1.

2.2. Preliminary neuropsychological examination

All the patients underwent a neuropsychological assessment, using a battery of standardized tests. As shown in Table 2, the performance of the AHG patients in the tests regarding general cognitive abilities (MMSE [23]; frontal assessment battery – FAB [3]; digit span and story recall [57]) was significantly worse than the performance of the CG (all t-tests p < 0.05 except story recall). It is worth noting, however, that three patients in the CG group also exhibited signs of mild deterioration (MMSE). Deficits of frontal functions as indexed from the FAB [3] were found in the AHG.

The frequency of extrapersonal (drawing on copy tests [67]), personal neglect (comb and razor test [40]) and visual and tactile extinction [1, 36] was greater in the AHG than in the CG. No significant differences were found between the groups in the Beck Depression Inventory (BDI [61]) and the State-Trait Anxiety Inventory (Form Y [55]). In addition, all patients underwent the Affective Recall Test (ART) [62], where they were asked to recall personal events that match a particular emotional category (e.g. “Try and recall an event in your life which caused you to feel anger or rage”). The control patients tended to link their emotions of fear and sadness to their disabilities (score 1 or 2). Interestingly, in keeping with previous reports [62], only one of the anosognosic patients referred their emotional experiences to illness; the others did not, even when asked specific, direct questions (score 0). In addition, behavioral and emotional reaction changes were evaluated by means of a short interview with the patients’ relatives (e.g. “Does the patient get angry more frequently now than before the illness?”). Referred emotional changes were reported for six patients, three for each group. It is worth noting that the Affective Recall Test is a verbal task, requiring declarative awareness of the disease and may not distinguish between cognitive and emotional deficits [54].

2.3. Assessment of anosognosia for hemiplegia

The neuropsychological assessment of AH aimed to investigate the existence of various forms of unawareness for motor deficits. The initial clinical interview used for categorizing the patients into two groups (with or without anosognosia for hemiplegia AHG and CG), consisted of the Berti and colleagues’ interview [10]. It was followed up with a modified version of the Marcel and colleagues’ interview [39] that was proposed to the groups with the aim of ascertaining the presence of various aspects of AH, namely: (a) general awareness of the disease; (b) awareness of the sensory-motor abilities of upper or lower limbs and (c) awareness of one’s own abilities in everyday activities (i.e. using a knife and fork, getting dressed, having a wash and walking). The CG patients did not show any signs of anosognosia in any of the interviews.

As shown in Table 3 (general interview), the patients exhibited varying degrees and forms of AH ranging from very mild to very severe deficits. The degree of anosognosia as indicated by the score in the Marcel et al. modified interview [39] did not correlate either with the interval from lesion onset (R = 0.3, p = 0.35) or with the interval from CT exam (R = 0.14, p = 0.68). While some patients presented with complete unawareness of paralysis and of its effects on the ability to carry out everyday activities, others were aware of specific sensory-motor deficits but unable to recognize the possible effects of their paralysis on everyday activities (e.g. patient TD). An examination of Table 3 also reveals different topographies of the deficit in the case
of three subjects (CB, DG, SA) who are more anosognosic for upper limb paralysis and for five subjects (CF, NC, SG, AG, GH) for lower limb paralysis.

In order to ascertain whether motor awareness deficits specifically involved one’s own body or also that of other people, AH patients were asked to report on their own abilities as well as, in a separate interview, about the abilities of another, known hemiplegic patient. In particular, AH patients were asked to report whether they were able to execute a series of complex actions (i.e. getting dressed, having a wash, cutting meat, walking, driving a car, hammering in a nail, kicking a ball, closing a mocha coffee pot, dancing, lighting a gas cooler). After an interval of 10–15 min, the patients were asked the same questions but referring to the performance of an age and gender matched hemiplegic patient who was seated in a wheelchair in front of them. This procedure allowed us to explore whether being anosognosic necessarily implies being unable to detect deficits in other individuals. Four of the patients (CF, DG, MD, GH) turned out to be anosognosic in the self-referred interview and seven others (CB, FG, NC, SG, TD, AG, PS) in both self and other-referred interviews.

Finally, an interview concerning the awareness of impairment in non-motor functions (i.e. sensory functions, neglect, memory, temporal orientation) was used to verify the specificity of AH. Four patients (DG, MD, NC, GH) were fully aware of their deficits in non-motor domains and thus showed a form of pure AH. In the remaining patients, AH was associated with defective awareness of neglect (6 out of 10), memory (4 out of 7) or temporal disorientation (3 out of 6).

It is worth noting that the patients’ scores in the interview concerning AH are not correlated to their performance in neuropsychological tests of general cognitive abilities, neglect, or emotional states (Pearson tests: all $p > 0.05$).

In conclusion, the neuropsychological assessment confirms that AH is a specific syndrome which is not directly dependent on mental deterioration or visuo-spatial and attentional disorders. Moreover, these data support the notion that anosognosia is a multifarious (rather than an all-or-none) syndrome where patients may exhibit awareness deficits involving different functions, various body districts, and one’s own body as well as that of others.

2.4. Lesion mapping

To explore the neural correlates of the various forms of residual motor awareness in anosognosia, we analyzed the lesions in patients with AH by using a voxel-based lesion-symptom mapping (VLSM) procedure, which allowed us to combine behavioral results with lesion-mapping techniques [5]. Lesions from CT scans were segmented and coregistered using a manual procedure with the MRlcro software (http://www.cabiatl.com/mricro/mricro/index.html) [52]. All the lesions were drawn on the slices of the current standard T1-weighted MRI scan template (ICBM152) from the Montreal Neurological Institute. This template is approximately oriented to match Talairach space [59]. The brain template was previously rotated on the midsagittal and midcoronal planes (pitch and roll) to match the orientation of the patients’ scans as well as possible. The scan images of the patient’s brain were then normalized and aligned (using digital image editing software) to superimpose onto the rotated template slices. Three experienced clinicians outlined the lesions on the rotated template, resulting in a map on which each voxel was labeled either 0 (intact) or 1 (lesioned). It is important to note that the lesion mapping was blind. Indeed, no clues indicating an association of a given

![Fig. 1. Overlay and comparison of AHG and CG lesions. Overlays of regional lesion plots of: (A) AH patients with right hemispheric lesion (MNI coordinates of the center of mass: $x = 33, y = -10, z = 22$); (B) controls (MNI coordinates of the center of mass: $x = 39, y = -10, z = 18$); (C) subtraction of the control group lesion plots from the AHG lesion plots (positive values center of mass: $x = 23, y = -14, z = 25$); (D) comparison of lesion plots related to AHG and CG (Liebermeister binomial measure FDR corrected: in green and yellow $L > 1.7, p < 0.05$; in red $L > 2.46, p < 0.01$, center of mass: $x = 30, y = -23, z = 16$); (E) FG lesion areas in the left hemisphere (center of mass: $x = -26, y = 3, z = 13$), involves mostly insula, caudate and putamen, and the white matter tissue between and around these structures. The number of overlapping lesions and the result of the subtraction are illustrated by different color coding for increasing frequencies, from purple to red. The same coronal (MNI coordinate: $x = 32$) and axial sections are shown in A–D. Additional details are provided in Table S1.](image-url)
lesion to a given patient were provided to any of the three clinicians. In a subsequent phase, the lesion maps were rotated back into a canonical orientation, using nearest-neighbor interpolation to restrict the map values to 0 and 1. All the lesion plots were drawn on the standard MNI space (2 mm × 2 mm × 2 mm). The area of each patient’s brain lesion was superimposed onto the T1 template to determine the total lesion volume and the involvement of various cerebral areas as calculated by MRicron (http://www.cabiatl.com/mricron/mricron/index.html) [53], by using the “automated anatomical labeling” template (AAL) [http://www.cytocore.ti/web/aal_anatomical_automatic_labeling.html] [60] and the “White matter parcellation map” (WMFP) template [41].

Table 2

Neuropsychological data in anosognosics (AHG) and controls (CG).

<table>
<thead>
<tr>
<th>Pt</th>
<th>MMSE</th>
<th>FAB</th>
<th>Verbal span</th>
<th>Story recall</th>
<th>Albert (40)</th>
<th>Copy (4)</th>
<th>TE</th>
<th>VE</th>
<th>Comb razor</th>
<th>BDI</th>
<th>STAI Y-1</th>
<th>STAI Y-2</th>
<th>AR (4)</th>
<th>RI</th>
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<td>CB</td>
<td>16.7</td>
<td>7.0</td>
<td>2.5</td>
<td>0.0</td>
<td>34</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>0.15</td>
<td>11</td>
<td>37</td>
<td>32</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>CF</td>
<td>21.9</td>
<td>6.8</td>
<td>4.0</td>
<td>10.0</td>
<td>6</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-0.53</td>
<td>7</td>
<td>47</td>
<td>42</td>
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<tr>
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<td>11.3</td>
<td>4.3</td>
<td>8.7</td>
<td>33</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>-0.83</td>
<td>12</td>
<td>43</td>
<td>45</td>
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<td>nf</td>
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<td>4</td>
<td>+</td>
<td>+</td>
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<td>10</td>
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<td>14</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<td>22</td>
<td>59</td>
<td>np</td>
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<td>–</td>
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<td>9.1</td>
<td>6</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<td>21</td>
<td>67</td>
<td>49</td>
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<td>1.2</td>
<td>4.0</td>
<td>2.8</td>
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The tests that show significant differences (p < 0.05) between the two groups.

Table 1

Demographic and clinical data of anosognosic (AHG) and nonanosognosic (CG) patients.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>G</th>
<th>Educ</th>
<th>Les Int</th>
<th>CT Int</th>
<th>Hand</th>
<th>Lesion site</th>
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<tr>
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<td>57</td>
<td>M</td>
<td>5</td>
<td>105</td>
<td>62</td>
<td>Right</td>
<td>FTP, BG</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>69</td>
<td>F</td>
<td>5</td>
<td>48</td>
<td>45</td>
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<td>P</td>
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Pt = patient; G = gender; Educ = education; Les Int = interval days between lesion onset and assessment; CT Int = interval days between lesion onset and the analyzed CT scan; Hand = handedness; Sens = sensory deficit; Mot = motor deficit; ± = deficit present; − = deficit not present; T = temporal; P = parietal; O = occipital; F = frontal; FTP = fronto-temporo-parietal junction; Th = thalamus; BG = basal ganglia. The two groups were matched for age, education, and interval between stroke and assessment (p > 0.05).
Table 3

| Awareness deficits as inferred from interviews. Higher scores indicate increasingly severe deficits. The questions concern: G = general conditions of illness; DLA = daily life activities; UL = upper limb paralysis; LL = lower limb paralysis; self and other refer to interviews in which patients reported on their own ability to perform a given action or about the same ability in another patient. The interview consisted of 10 questions, each asked twice (once for the self and once for the other condition). For each question, defective reports are scored 1. A maximal defective score of 10 for each condition could be obtained. |
|---|---|---|---|---|---|
| General interview | Self/other interview |
| | G | DLA | UL | LL | TOT | Self | Other | S&O |
| CB | 2 | 3 | 7 | 4 | 16 | 5 | 0 | 4 |
| CF | 1 | 4 | 6 | 8 | 19 | 10 | 0 | 0 |
| DG | 2 | 3 | 8 | 5 | 18 | 5 | 0 | 1 |
| FG | 1 | 4 | 5 | 6 | 16 | 6 | 1 | 3 |
| MD | 3 | 4 | 7 | 6 | 18 | 10 | 0 | 0 |
| NC | 2 | 4 | 8 | 17 | 3 | 0 | 0 |
| SA | 1 | 3 | 7 | 3 | 14 | np | np | np |
| SG | 2 | 3 | 4 | 8 | 17 | 5 | 0 | 4 |
| TD | 0 | 4 | 0 | 0 | 4 | 2 | 1 | 2 |
| AG | 2 | 4 | 17 | 15 | 0 | 4 | 6 |
| GH | 1 | 4 | 5 | 7 | 17 | 6 | 0 | 0 |
| PS | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

The subtraction technique and the VLSM procedure based on the Liebermeister binomial test false discovery rate (FDR) corrected were used for the comparison of the damaged areas between anosognosic and non-anosognosic subjects.

In addition, t-test statistics were computed for the group of 11 AH patients with right hemispheric lesion using the continuous behavioral measurements in the various tasks (i.e. scores in the self and other referred interview concerning anosognosia, scores in the implicit and emergent awareness tasks) as predictors. All the statistical comparisons were performed for each lesioned voxel of the brain [53]. Colored VLSM maps were produced that represent the t-statistics of the voxel-wise comparison between patients with or without lesion on a given voxel. The maps indicate the voxels at which patients with a lesion in a given voxel performed worse than patients without lesion to that voxel on specific behavioral measurements concerning various tasks. The alpha level of significance was set at $p < 0.05$ and was corrected for multiple comparisons by using the false discovery rate (FDR) threshold.

2.5. Experimental tasks

To assess whether the attempt to execute a given action may improve motor awareness deficits in AH patients, we developed two different tasks modified by previous studies [29,39,40–51]. The tasks aimed to explore whether any changes in awareness contingent upon the attempt to perform an action occurred at implicit, explicit, or both levels. The order of the two tasks was counterbalanced. Voxel-based lesion analysis allowed us to explore any causal association between lesioned brain areas and scores in the tasks tapping different forms of body awareness deficits.

2.5.1. Task 1: implicit awareness

The situation in which patients who verbally deny their paralysis but act as if they know they cannot move the paralyzed body part (e.g. their arm) is here called implicit awareness. This type of awareness is observed in patients who, although they state they can perform a given action (e.g. walking), seek help when trying to act.

2.5.2. Procedure

Our task was developed by capitalizing on the first clinical reports of “tacit knowledge” [51] and on a study concerning patients affected by spatial neglect [29]. A dissociation between implicit and explicit awareness in hemiplegic right damaged patients has been reported in a recent study [16]. However, the two forms of awareness were investigated by means of two different tasks, namely the VATAm test for explicit awareness and the attempt to execute binomial actions for implicit awareness [16]. Here we report the dissociation in the same task thus ruling out any spurious effect due to possible across-tasks difficulty differences.

Subjects were comfortably seated in a quiet room and the examiner sat in front of them. They were asked to reach for and grasp a large object and hold it in a horizontal position. Five different objects were used (wooden rod, basin, umbrella, tea-tray, saucepan). Given the features of the objects (Table 4), grasping and holding them required the use of both hands or, in the case of using one hand, grasping the center of the object. Moreover, the request to hold them in a horizontal position along their longer axis made it very unlikely that under normal circumstances the objects could be grasped at their handle.

The task was carried out in three consecutive steps: in a preliminary interview the objects were shown to the patients who were asked to state how many hands they would use for raising and holding them in a horizontal position (first step). If, in spite of the paralysis, the subjects declared that they could use two hands (and only in this case), the examiner demonstrated the action t to the patients using both hands (second step). They were then asked to actually pick up the objects (third step). For patients showing neglect, the objects were presented in their right hemispace. Each object was presented four times according to a randomized order and in different spatial orientations. The distance between the position of the patient’s non-plegic hand and the right hand edge of the object was measured and recorded. Shifts of the grasp towards the midpoint of the object were measured (in mm) using the position of the thumb. Given the different length of the objects, percentage scores were used. Shifts towards the object’s midpoint index implicit awareness (cut-off: 25% of the length of the object; 0 = extreme right; 50% = center of object; 100% = extreme left).  

3. Results

All control patients declared they were unable to move their left hand and held the test objects using only their right hand placed at the center of the object. In contrast, AH patients declared that they were able to use both hands. When executing the requested action seven out of 12 positioned their right hand at the extreme right of the object, coherently with their verbal report. It is important to note, however, that five patients (CB, CF, DG, FG, TD) shifted their hands towards the central position when grasping/holding at least three objects (mean of scores >25%, see Table 4). This discrepancy between the verbal report and the grasping/holding action indicates the presence of implicit awareness. Using the modified t-test procedure and the Bayesian Standardized Difference Test (BSDT) [20], which are designed to analyze single patient data, we compared the performance of each of these five patients with the performance of the AH patients who did not show implicit awareness. Significant or marginally significant shifts towards the object midpoint were found in each of the five patients (all $p < 0.05$; $p = 0.067$ in patient CB). No other differences among the other members of the AHG were found (all t-test $p$ (one tailed) > 0.1). Table 4 shows the mean scores of the patients’ hand positions for each object.

Thus in subjects with implicit awareness right hand performance was implicitly conditioned by the presence of left side paralysis despite the total absence of linguistic/declarative awareness of the deficit. Although these patients verbally denied their left arm paralysis, they shifted their grasp towards the center of objects as if they knew that this was the only possible way of performing the grasp/hold action unimanually. This is similar to the behavior of hemiplegic non-anosognosic patients with the fundamental difference that the latter verbally report their deficit during the interview. Two other patients (NC, AG) did not show any signs of implicit awareness, picking up all the objects at the extreme right end, as if they really could use their left hand too. The remaining five subjects (MD, SA, SG, GH, PS) tended to shift their grasp towards the center of the object in the case of the umbrella and/or the wooden rod, while their hand was positioned on the extreme right with the other objects. It is plausible that in these patients the length of the
umbrella and wooden rod shifted their attention towards the left. In this case their behavior might be an index of increasing spatial awareness rather than of awareness of paralysis [29].

PS’s performance deserves specific comments. Although in the AH interview he appeared to be quite aware of his paralysis (score 1/23), in this task he always declared that he was able to use both hands and he behaved as if he was unaware of his paralysis. The Crawford procedure confirmed that performance of patient PS dissociates from other patients in the interview for AH (t(10) = 3.44, p(one tailed) = 0.003), but not in the implicit awareness task (t(10) = −0.55, p(one tailed) = 0.295). Thus, an unusual dissociation with preserved verbal awareness and lack of implicit awareness was found in this patient. The lesional analysis shows that although largely overlapping with that of the other anosognosic patients, PS’s lesion extended more medially and ventrally (Fig. S1).

To exclude the possibility that visuo-spatial neglect may influence patients’ behavior leading them to grasp objects at the extreme right end, 5 out of the 6 non-anosognosic control patients who exhibited neglect were asked to perform the task. All the patients declared they could use only their right hand. As shown in Table 4, they grasped the objects in a central position. Thus, the positioning of the hand at the right of the object observed in some AH patients is not related to the presence of spatial neglect.

### 3.1. Task 2: emergent awareness

We define emergent awareness as the condition in which a patient denies his/her motor deficits but becomes linguistically aware of them when asked to actually perform an action using the affected body part. We designed a task modified by a previous study [39] aimed at testing whether emergent awareness can be evoked in patients with anosognosia for motor deficits by asking them to attempt to execute a given action. This would provide evidence that action execution can increase declarative awareness.

#### 3.1.1. Procedure

The patients were asked to execute five bimanual actions (tying a knot, closing a mocha coffee pot, clapping, cutting a piece of paper, and dealing cards) and five unimanual actions (writing a word, brushing teeth, turning over the pages of a magazine, combing hair, pouring water into a glass). No specific instruction about which hand should be used for unimanual actions was given. Moreover, they were asked to judge the proficiency with which they could perform each action before, during, and after the attempt to actually perform the action. Three judgments were thus obtained for each action. The order of the unimanual and bimanual actions was randomized. The verbal responses were scored as follows: 3 = correct judgment before the request to perform the action; 2 = correct judgment only when subjects were about to start the action; 1 = subjects became aware of their deficits after failure of the action; 0 = the awareness of paralysis did not improve after the failed attempt to execute the action. Changes in the patients’ judgment of proficiency (before, during, and after attempt to perform the action) in performing the bimanual actions provided an index of emergent awareness. A comparison of the performance of the AH group with the CG scores was not possible since the non-anosognosic subjects were aware of the fact that bimanual actions were impossible to realize. Thus with the aim of discriminating patients with emergent anosognosia with respect to the others, we analyzed the distribution of the AH group’s scores. A mean score over the third quartile was considered an index of emergent awareness (Table 5).

### 4. Results

Control subjects always answered appropriately, typically declaring that they were unable to perform bimanual actions, but able to carry out unimanual actions based on the use of the right upper limb. AH patients declared they could perform unimanual and bimanual actions without any problems. Unimanual actions were always performed with the right hand and were thus errorless. For the questions concerning bimanual actions, three out of the 12 AH patients (NC, SG, AG) showed emergent awareness. Indeed, their mean scores fell over the third quartile (3 Q = 7.25; all t-test p(one tailed) = 0.02; Crawford t-test [20]). Note that all these patients were able to detect their deficits for at least three different actions before or during the attempt to execute them. On the contrary, three patients (SA, TD, GH) did not show any change of awareness related to intention or attempt to execute actions. The remaining patients (CB, CF, DG, FG, MD, PS) showed instances of increased awareness on one or two occasions (Table 5).
To sum up, although most of the anosognosic patients exhibited scarce linguistic awareness, the attempt to execute actions increased motor awareness in at least some of them. Note that patients with emergent awareness are not the same as those with implicit awareness. Rather, as indicated by the significant negative correlation between the scores in the two experimental tasks \((r = -0.68, p = 0.014)\), defective performance in one task might be associated with good performance in the other. Therefore, the two tasks appear to tap different abilities and to highlight different forms of deficit in motor awareness.

4.1. Results of lesion mapping

4.1.1. Damaged areas related to anosognosia for hemiplegia

The comparison between damaged areas in anosognosic and non-anosognosic patients shows that overall lesion volumes did not differ in the two patient groups (AHG mean = 147 cc, SD = 109; CG mean = 155 cc, SD = 130; \(t_{22} = 0.16, p = 0.88\)). Fig. 1 shows the overlay lesion plots of the AHG (Fig. 1A) and the CG (Fig. 1B). The subtraction of the superimposed lesions of the CG from the overlap image of the AHG (Fig. 1C) and the statistical comparison between the two groups (Liebermeister binomial measure FDR corrected, Fig. 1D) show that cortical and subcortical areas in frontal (rolandic operculum, insula), temporal (hippocampus and temporal superior) and fusiform cortex, the cingulum, the caudate, and the thalamus are significantly more damaged in the AHG as compared to the CG (see also Table S1). These data are consistent with previous studies [8, 36, 65] and confirm the validity of the measures used to identify and classify anosognosic patients.

No correlation between total lesion volume and scores in the interview was found \((r = 0.45, p = 0.14)\) in the AHG. This rules out the possibility that the severity of anosognosia is simply caused by the extension of the lesion.

Instead, it is worth noting that there was a positive association between defective performance in the interview (Table 3) and lesions to the insula, the rolandic operculum (two regions associated with AH according to previous reports [9, 36]) and the superior temporal cortex. Although based on CT scans, that do not allow precise estimations of white matter, our lesion analysis shows the involvement of the subcortical white matter in the region of the superior region of corona radiata and the superior longitudinal fasciculus (Fig. 2A).

4.1.2. Self-referred vs. other-referred deficits

The lesional analysis (see the caption to Fig. 3 for details) comparing patients with self-referred vs. self- and other-referred deficits, revealed in the former group greater involvement of frontal inferior areas, rolandic operculum, insula, temporal superior cortex, caudate, and putamen, as well as the white matter involving the external and internal capsule, the superior corona radiate, the inferior fronto-occipital fasciculus and the corticospinal tract. Regions associated with deficits in the self and other condition encompass the regions around the central sulcus, parts of the frontal inferior and superior areas and the supplementary motor area (Fig. 2B and Table S2).

4.1.3. Lesional correlates of deficit in implicit and emergent awareness

It is important to note that different neural regions seem to underpin the two forms of lack of awareness highlighted in the present study.

The impaired performance in the implicit awareness task results causatively associated with damage to the middle temporal cortex and the white subcortical matter anterior to basal ganglia, probably involving the superior region of corona radiata and the superior longitudinal fasciculus (Fig. 3). On the contrary, lack of emergent awareness turns out to be causally associated with more posterior and cortical structures (e.g. rolandic operculum, the insula and the superior temporal cortex; details in Fig. 3). The lesion analysis of PS, the patient who presents with a specific lack of implicit awareness, shows that although largely overlapping with that of the other anosognosic patients, his lesion extends more medially and ventrally (Fig. S1).

We want to note here that some of the dissociations highlighted by the VLSM (e.g. implicit vs. emergent awareness, anosognosia interview, first and third person) are shown in a small number of patients. Consequently, the statistical power of these analysis may be low and the results need to be confirmed by further investigations.

5. Discussion

Mounting evidence indicates that anosognosia for hemiplegia is a multifarous syndrome [45, 63, 66] in which tacit knowledge about deficits not acknowledged linguistically may exist [39, 43]. Previous studies hint at the existence of implicit forms of awareness [49–51]. However, only recent studies have started to explore systematically the syndrome beyond the most commonly used scales [16, 24, 26]. In addition, lesion mapping studies have highlighted the cerebral underpinnings of AH [9, 35]. Here we expand previous knowledge by showing that AH is expressed in various degrees of severity and forms (i.e. a specific deficit of awareness for the plegia in the supe-
Patients involved in ALS and VLSM to involving sulcus, the posterior
Fig. 2. Regions associated with various clinical forms of anosognosia. Regions associated with: (A) higher severity of AH (as inferred from the general interview). The main lesional cluster (center of mass, \(x = 43; y = -2; z = 9\)) involves the insula, the rolandic operculum, frontal inferior and temporal superior areas and the white matter pertaining to the superior corona radiata and the superior longitudinal fasciculus. (B) Deficits in estimating motor deficits in the self and other conditions. As detailed in Table 3, four patients exhibited selective deficits in estimating motor deficits in the self-condition. In the remaining patients, estimation deficits, although predominant for the self, also involved the other condition. Two indices of prevalence of errors in the self \(\{\text{self} - (\text{other} + \text{both})\}\) vs. self and other \(\{(\text{other} + \text{both}) - \text{self}\}\) were computed and entered into two VLSM analyses as independent predictors. Regions associated with deficits associated solely with the self involve the putamen and caudate to the insula, the frontal inferior and the temporal superior areas, and the white matter involving the external and internal capsule, the superior corona radiate, the inferior fronto-occipital fasciculus and the corticospinal tract (blue gradation, center of mass: \(x = 34, y = 3, z = 6\)). Regions associated with deficits in the self and other condition involve the areas around the central sulcus, the pars of the frontal inferior and superior areas and the supplementary motor area (yellow gradation, center of mass: \(x = 28, y = -3, z = 43\)).

rior or inferior limb, the unawareness of the consequences of the paralysis in daily life), and may also affect different body parts.

In our study, AH patients were more cognitively impaired than non-anosognosic patients, particularly in tests tapping frontal abilities. This is in keeping with a recent study in patients affected by Alzheimer’s disease where a link between impairment in cognitive flexibility and awareness of deficits was found [2].

A clear double dissociation between explicit and implicit awareness for motor deficits has been demonstrated by comparing verbal report measurements and requests to actually perform actions [16]. Moreover, lack of explicit awareness of hemiplegia in the presence of implicit awareness of it has been demonstrated by asking patients to perform a stroop-like inhibition task where the test material contained deficit-related information as well as other neg-

Fig. 3. Regions associated with lack of residual awareness. In particular, absence of implicit awareness seems to be associated with three lesional clusters (in red): one involving the superior corona radiating around the genu of corpus callosum (MNI coordinates of the center of mass: \(x = 22; y = 23; z = 24\)), the second involving the superior longitudinal fasciculus (MNI coordinates of the center of mass: \(x = 31; y = -1; z = 31\)) and the other involving the temporal middle (MNI coordinates of the center of mass: \(x = 56; y = 28; z = -38\)). Lack of emergent awareness was associated with lesions involving the insula, rolandic operculum, superior temporal gyrus; the white matter includes the corticospinal tract, the posterior and superior corona radiate (in yellow; MNI coordinates of the center of mass: \(x = 33; y = -29; z = 23\)). The table associated with this figure shows for each region: the number (N) and the percentage (N%) of clustering voxels that survived the threshold of \(p < 0.05\) (false discovery rate corrected); the maximum t-test (t) Z statistic obtained for each cluster; the MNI coordinates of the center of mass.
whereas or neutral information [24]. Unlike previous reports [16,24] we investigated the implicit/explicit dissociation using the same motor task. This allowed us to rule out the influence of spurious variables like degrees of difficulty or different cognitive processes involved in different tasks and to demonstrate how the attempt to act may disclose different levels of awareness.

Moreover, we have expanded previous knowledge by devising two tasks exploring not only the dissociation between explicit and implicit processing but also two different forms of residual awareness for hemiplegia, namely implicit and emergent awareness. In addition, by combining behavioral results with advanced lesion mapping procedures, we explored the neural circuits underlying any differential residual awareness. Two key results were obtained. The first is that the attempt of AH patients to execute actions may elicit different forms of previously unexpressed awareness. The second is that the lack of two different forms of awareness is causatively associated with lesions in different nodes of the body awareness cerebral network. Furthermore, our experiment revealed that lack of explicit awareness of motor deficits may occur for self but not for others’ deficits and that this dissociation is underpinned by different neural substrates.

5.1. Performing actions or attempting to perform them discloses different forms of residual awareness in AH

Recent studies have addressed the issue of implicit versus explicit forms of motor awareness by distinguishing declarative and non-declarative knowledge of the deficit [16,24,43,65]. In the present study we sought to determine whether acting or trying to act influences AH at implicit, explicit levels or at both levels.

5.1.1. Implicit awareness

In our first experimental task, devised with the aim of highlighting the presence of implicit awareness, AH patients were required to perform actions that implied the use of both hands. Although these patients typically declare they are able to execute an action using two hands, they may successfully implement the same action using only one hand, e.g. positioning the intact hand towards the center of large objects so as to make unimanual movements possible. This pattern of behavior indicates that patients acknowledge their paralysis at some non-verbal levels of awareness. Within the feed-forward model framework [30], the presence of implicit awareness suggests that in spite of loss of verbal awareness, the putative neural system for matching somatic information about the paralysis and motor planning, the so-called comparator, may be still functioning in some anosognosic patients. In contrast, absence of implicit awareness would hint at a failure of the comparator so that patients plan their actions as if they can actually move both hands. This hypothesis agrees with the results of a single case study where the deficit in detecting discrepancies between the actual and predicted states of the intact arm is interpreted as a change in the efficiency of the comparator system. This purported deficit in detecting action errors did not allow the comparator system to update action programs and to make on-line corrections [47].

This hypothesis is consistent with the multicomponent model of anosognosia for hemiplegia. Vojat and Vuilleumier [64] suggest the existence of two parallel monitoring systems, that work at implicit and explicit levels respectively. The implicit system (also considered the system for motor error processing) is thought to be based on the automatic monitoring of the affective relevance of mismatch between goal and outcome. In contrast, the explicit system deals with conscious error detection and is based on the quality of the feedback and on the access to attentional and executive network. Interestingly, while the implicit system is more linked to subcortical structures, the explicit one is linked to the fronto-parietal cortices.

Previous studies suggest that the bizarre answers of AH patients to questions regarding their paralysis might represent a defence mechanism (repression) to avoid the pain of acknowledging the pathological condition [61,62]. In keeping with this suggestion is the result that attention is preferentially captured by illness-linked words in non-anosognosic brain damaged patients but not in anosognosic subjects [43]. In particular, while reduced response latency to emotionally threatening words were found in non-anosognosic patients, increased response latency to the same stimuli was found in anosognosic subjects. This suggests that the specific inhibitory effect for words related to the disease may close implicit knowledge of deficit. It has also been suggested that AH is influenced by the disruption of the right hemisphere emotion-regulation system such that these patients are less able to tolerate the burden of their post-lesional condition [62]. In keeping with this hypothesis is the result showing that our AH patients are unable to link their emotional state to their illness. It may be worth noting that the emotional flatness linked to AH which emerges when patients are asked to describe their feelings contrasts with the report of patients’ relatives indicating these patients are in fact able to detect emotions. This result may be in keeping with the notion that anosognosic patients show specific difficulties in describing their feelings, but not in identifying them [54].

5.1.2. Emergent awareness

In our second experimental task, devised with the aim of highlighting the presence of emergent explicit awareness, AH patients were required to try and perform specific actions and then to verbally report their proficiency in actually doing the task. It is important to note that the request to report on their performance was made before, during, and after each attempt to perform the action. Results show that intending to act and/or actually acting may modify explicit, verbal knowledge of the deficit in some AH patients. It is also worth noting that no change in paralysis awareness was recorded before and after the neuropsychological screening tests, thus hinting at the specific role of our experimental task in modulating the ability to become linguistically aware of one’s own motor disorders. Studies indicate that normal motor awareness is based on the congruence between action planning and the prediction of the sensory consequences of the same action [12,27]. According to this ‘forward dynamic model’, when a given movement does not occur as intended and planned, a mismatch between predicted and actual sensory feedback is detected by a brain comparator that brings about conscious awareness of an error [8]. Thus, the quintessential feature of AH, namely the loss of verbal awareness concerning one’s own motor disorders, may be due to defective functioning of the comparator [36]. Intention to act may play an important modulatory role as regards the system for monitoring discrepancy between prediction and actual sensory feedback. It has been shown, for example, that at least some AH patients, when requested to move the paretic arm, do not try to contract their muscles, thus manifesting a loss of motor intention [28]. This is at variance with what has been reported in a hemiplegic patient with AH who exhibited left proximal muscle activation even though left-side reaching movements could not be performed [7].

The possible role of intention to move in modulating motor awareness in AH patients has been tested systematically in a series of recent studies (see [34], for a review). In particular, the hypothesis that motor awareness is more related to intentional motor planning than to sensory feedback has been tested in an ingenious experiment where hemiplegic patients, with or without AH, were asked to raise their paralyzed left arm (self-generated movement), or were told that the arm was to be lifted by an examiner (externally generated movement) [26]. Since the patients were unable to move their hand, a naturalistic rubber model of the left arm was used in order to provide false visual feedback about any left-hand move-
ment. While the patients’ arm was out of view, the rubber hand was visible and anatomically aligned with the patient so as to be perceived as belonging to her/him. In different trials an experimenter moved the rubber hand or kept it still thus creating a congruence or an incongruence with the patients’ intention to move. The patients’ task was to detect whether or not the rubber arm had moved. High levels of accuracy were also found in AH patients with the exception that they gave a lot of false alarms in the self-generated movement condition where they reported movements of the rubber arm which had however remained still. This pattern of results indicates that motor intention may predominate over visual feedback. The idea that intention to move may worsen motor awareness seems at odds with our results. However, in our conditions increased linguistic awareness of motor disorders contingent upon the intention to act mainly arose from the confrontation with the failure to act. Although the functional mechanisms of this effect are currently unknown, we speculate that intention to act combined with the confrontation of the failure to act may bring about an amelioration of the defective system that matches prediction with expected and actual sensory consequences of actions. The possible neural correlates of this effect are discussed in the next section.

5.2. Neural circuits underlying AH and different forms of residual motor awareness

It is now widely held that AH may be underpinned by lesions in a large and complex cortico–subcortical network [46,65]. In keeping with recent reports, we show that the frontal inferior cortex, the temporal cortex and the hippocampus cortex are lesioned in AH patients. Also the insula, a neural structure involved in body awareness [19], seems to be crucial for awareness of body movement [9,36]. Interestingly, our lesion mapping analysis provides novel evidence on the neural correlates of different forms of residual motor awareness. In particular, it indicates that lack of implicit awareness is associated with lesions involving the middle–temporal cortex and the white subcortical frontal matter anterior and around the basal ganglia. This is consistent with the Vocat and Vuilleumier model [64] and previous experimental data [24] according to which basal ganglia, amygdala, insula and anterior cingulated cortex are linked to implicit awareness.

Note that patient PS, who exhibited explicit but not implicit awareness, presented more extensive subcortical involvement than the other AH patients. This result seems to be in line with the important role of these regions in non-declarative learning that typically occurs at implicit levels. In contrast, although the sensitivity of CT images is high enough to identify the single white matter tracts, it seems that the sites which are significantly associated with lack of emergent awareness involve the antero–posterior tracts of white matter connecting bidirectionally the parietal cortex and the precuneus. Indeed functional imaging studies in healthy subjects indicate that the precuneus and the inferior parietal lobe may play a role in self-consciousness in the visual guidance of hand movements and probably also in the awareness of action [15,31]. Thus, while lack of implicit awareness may be linked to lesions of the fibres connecting the basal ganglia and the frontal cortex, lack of emergent explicit awareness may be linked to lesions of pathways connecting the parieto–temporal and frontal cortices.

5.3. Lack of explicit awareness for self versus others’ motor deficits and its lesional basis

Exploring the variables that can modulate changes in verbal awareness has both theoretical and practical implications. We focused on the first vs. third person perspective and the self vs. other dimension [49,50,63]. The dramatic recovery from severe AH in a woman who saw herself in a video [25] suggests that self-observation from the outside is dissociated from first person perspective observation, possibly at both phenomenological and neural levels. In keeping with previous investigations [39,49,50], we show that at least some AH patients, although totally unaware of their own paralysis, are able to identify motor deficits in other people. However, while three AH patients exhibited exclusive deficits for the self, none of them exhibited exclusive deficits referring to others. Thus it seems likely that motor awareness deficits are not related to actions per se but to defensive awareness of one’s own body actions. Further insights into the nature of first vs. third person awareness deficits come from the lesional analysis. Lack of first-person awareness seems to be linked to damage to a large cerebral network (frontal inferior, Rolandic operculum, superior temporal cortices, insula, putamen and caudate), largely overlapping the one underlying typical body awareness disorders such as somatoparaphrenia [13,42]. Third-person awareness disorders seem to be associated with regions involved in the perception and planning of action, such as the motor and premotor areas.

In conclusion, our study expands previous knowledge by investigating the experimental conditions that trigger implicit and explicit residual forms of motor awareness and by showing that they rely upon at least partially different neural substrates.

Unfortunately only CT images (and not MRI) were available for the lesional mapping analysis. This may reduce the specificity of the discussion about the link between lesions involving different parts of white matter tracts and different forms of anosognosia. Moreover the interval between lesion onset and CT exam is variable in both groups. However, it is worth noting that control group patients did not exhibit any signs of anosognosia in the acute phase while anosognosic patients did present disorders of awareness also in the sub–acute and/or chronic phases. In view of this, our results may have implications for rehabilitation. Indeed, they show that the diagnosis of anosognosia for hemiplegia needs various methods of assessment to identify specific aspects of awareness and its disorders. Targeting and selecting therapeutic strategies should be based on a precise diagnosis. Our data suggest that relying on residual implicit awareness recover of motor disorders may be accelerated in some patients and that the attempt to act may promote explicit awareness in some other patients. Therefore, these notions may support the identification of new individual strategies. Moreover, as suggested by a previous case report, recognition of paralysis in others but not in self indicates that rehabilitative training of self-observation in a third person perspective by means of a mirror or a video may be possible [25].

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Appendix A. Supplementary data

References