‘Moving’ a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia

Garbarini F; Rabuffetti M; Piedimonte A; Pia L; Ferrarin M; Frassinetti F; Gindri P; Cantagallo A; Driver J; Berti A. 'Moving' a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia. BRAIN. 135 (5) pp: 1486-1497.
DOI: 10.1093/brain/aws015

'Moving' a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia

Francesca Garbarini, Marco Rabuffetti, Alessandro Piedimonte, Lorenzo Pia, Maurizio Ferrarin, Francesca Frassinetti, Patrizia Gindri, Anna Cantagallo, Jon Driver and Anna Berti

Selective neurological impairments can shed light on different aspects of motor cognition. Brain-damaged patients with anosognosia for hemiplegia deny their motor deficit and believe they can still move the paralysed limb. Here we study, for the first time, if the anomalous subjective experience that their affected hand can still move, may have objective consequences that constrain movement execution with the opposite, intact hand. Using a bimanual motor task, in which anosognosic patients were asked to simultaneously trace out lines with their unaffected hand and circles with their paralysed hand, we found that the trajectories of the intact hand were influenced by the requested movement of the paralysed hand, with the intact hand tending to assume an oval trajectory (bimanual coupling effect). This effect was comparable to that of a group of healthy subjects who actually moved both hands. By contrast, brain-damaged patients with motor neglect or actual hemiplegia but no anosognosia did not show this bimanual constraint. We suggest that anosognosic patients may have intact motor intentionality and planning for the plegic hand. Rather than being merely an inexplicable confabulation, anosognosia for the plegic hand can produce objective constraints on what the intact hand does.

Keywords: action monitoring; anosognosia; brain damage; intention; interlimb coordination

Abbreviations: AHP = anosognosia for hemiplegia

Introduction

A challenge for neuroscience is to understand the conscious and unconscious processes underlying construction of willed actions. Many of the processes that produce a motor act are not accessible to consciousness. Nevertheless, we are usually aware of our motor intentions and we have motor awareness of whether we are actually moving part of our body. But some neurological patients believe they can still act out their motor intentions even for body parts that are actually paralysed.

Anosognosia for hemiplegia (AHP) is a clinical condition in which movement awareness seems dramatically altered. First described by Austrian (Anton, 1898, 1899), German (Pick, 1898) and Swiss (Zingerle, 1913) neurologists, the phenomenon was named 'anosognosia' (from Greek for 'lack of knowledge for the illness') in 1914, by the French neurologist Joseph Babinski (Babinski, 1914). AHP is usually observed in patients with right-brain damage who obstinately deny that there is anything wrong with their contralesional limbs, despite the presence of severe left paralysis (Pia *et al*., 2004; Orfei *et al*., 2007; Vocat *et al*., 2010). When questioned about their capability of performing actions with the right or left hand, or even bimanual actions, patients with AHP characteristically claim that they can perform any kind of movement equally well. If asked to produce an action with the paralysed limb, some patients appear convinced that they are actually performing it (Supplementary Videos 1 and 2) although sensory and visual evidence from the affected motionless side should indicate that no movement has in fact been performed (Berti *et al*., 2006, 2007; Jenkinson and Fotopoulou, 2010). Many different accounts have been put forward to explain this striking phenomenon, ranging from psychodynamic/emotional theories (Weinstein and Kahn, 1950, 1955; Spalletta *et al*., 2007) to more neuropsychological explanations.

According to psychodynamic accounts, AHP is not considered a disturbance related to a direct effect of the brain damage, calling for a neuropsychological explanation, but instead is a motivational reaction against the stress caused by the illness (Weinstein and Kahn, 1955). Although motivational factors alone cannot account for all aspects of AHP (Bisiach and Geminiani, 1991), the possibility that at least some forms of denial are driven by motivational reactions has recently been reinvigorated by Nardone *et al*. (2007). They found an interference effect in an attention-capture test for words associated with hemiplegia-related deficit in patients with AHP and interpreted this result as evidence of an implicit knowledge of the disease involving repression mechanisms.

Neuropsychological explanations typically consider AHP as a more cognitive deficit directly caused by brain damage, albeit a potentially heterogeneous condition. AHP has often been explained away as the consequence of many neurological/neuropsychological deficits co-occurring to prevent the patients from discovering their contralesional motor problems (Levine *et al*., 1991; Feinberg, 1997; Vuilleumier, 2000, 2004; Vallar *et al.,* 2003; Gialanella *et al.,* 2009). This might apply for some cases, although double dissociations have been reported between AHP and various other neurological/neuropsychological disorders. Some authors (Marcel *et al*., 2004; Cocchini *et al*., 2010; Fotopoulou *et al*., 2010) argue that different patients with AHP may have distinct cognitive impairments, possibly reflecting differences in the location and extent of brain damages (which may also differ between acute versus more chronic cases; see Vocat *et al*., 2010).

Several authors have proposed that, at least in some cases, AHP may be conceptualized as a selective disorder of motor cognition (Gold *et al*., 1994; Frith *et al*., 2000; Berti *et al*., 2005; Coslett, 2005; Fotopoulou *et al*., 2008; Jenkinson *et al*. 2009; Bottini *et al*., 2010) related to recent computational models of motor production and motor control (Wolpert *et al*., 1995; Blakemore *et al*., 2002; Haggard, 2005). Such models posit that intentions to move and the corresponding motor commands normally lead also to a prediction (forward model) of the sensory consequences for the planned movement. According to Blakemore *et al*. (2002), this prediction would be subsequently matched (by a 'comparator' system) to the actual sensory feedback consequent on moving, leading to motor awareness. If the intended movement is not actually performed, the comparator should detect a mismatch. Within this context, two different proposals have been put forward to explain certain aspects of AHP. According to some views (Heilman, 1991), the brain damage in patients with AHP may causes an inability to form motor intentions and plans. If intentions to move are defective, motor planning will not arise, and so the comparator (even if intact) will not receive information about movement planning, hence cannot interpret the lack of movements as aberrant. As a consequence, the patient may be unable to discover that he/she is plegic (feed forward hypothesis; Adair *et al*., 1995; Heilman *et al*., 1998; Coslett, 2005). The absence of activation of proximal muscles on the affected side when the patient is requested to make a movement has been taken as evidence for such a lack of motor intentions (Gold *et al*., 1994). However, other studies showing the opposite pattern of results for proximal muscles (Hildebrandt and Zieger, 1995; Berti *et al*., 2007) leave the question of the impairment of intentional processes in AHP still unresolved.

An alternative view considers AHP as potentially due to damage to the proposed 'comparator' system (Berti *et al*., 2005; Berti and Pia, 2006). This would impair the motor monitoring process preventing patients with AHP from distinguishing between movement and no-movement states. Interestingly, some of the regions thought to be involved in motor intention and planning operations (usually involving frontomesial and parietal circuits: Libet *et al*., 1983; Haggard and Magno, 1999; Lau *et al*. 2004; Desmurget *et al*., 2009; Fried *et al*., 2011) are typically spared in AHP, as for the supplementary motor area and the pre-supplementary motor area (Berti *et al*., 2005).

The present study took a novel approach to the nature of experienced but unexecuted movements by the plegic hand in AHP. Specifically, we sought to determine if being requested to make particular movements with the paralysed hand could actually have 'objective' consequences for real movements performed concurrently with the opposite, intact hand. Note that if such objective consequences were indeed to be found, this would imply that the requested movements with the paralysed hand had indeed been intended and internally planned by the patients with AHP on request, in the specific sense that these (actually impossible) movements impact objectively upon what the intact hand can do. In contrast, if the patients with AHP can neither intend nor plan movements for the plegic side (as proposed by some accounts, see above), there should presumably be no impact on the intact side.

While blindfolded, our participants had to draw circles and lines, either performing unimanual drawing movements (the right hand drew unilateral lines, 'Unimanual Lines') or bimanual movements (the right hand drew lines and simultaneously, the left hand drew circles; bilateral circle-line, 'Bimanual Circles-Lines'). Franz and colleagues (1991) found that in normal subjects there is a bimanual interference (coupling) effect when non-congruent movements are

performed by the two hands. The trajectory of the hand which should draw lines tends to assume an oval shape (i.e. more spatial error) when the other hand must concurrently draw circles, compared to unimanual conditions, indicating that the motor programmes for the hand drawing circles can affect the motor programmes of the hand drawing lines, to produce a bimanual interference effect.

We predicted that, if patients with AHP do intend and plan movements with their paralysed hand, the lines drawn by the intact hand should become more oval when the patients are requested to draw a circle concurrently with their plegic hand, as found in normal subjects. We compared performance of three right-hemsiphere-damaged patients with AHP (see below for case details) against 10 neurologically intact subjects in the bimanual drawing task.

We further compared the patients with AHP with two other types of neurological case. We assessed five hemiplegic but non-anosognosic right-hemisphere-damaged patients. Like the patients with AHP, the hemiplegic cases could not move their left plegic hand. But unlike the patients with AHP, the hemiplegic cases were fully aware that they could not move their contralesional hand. The contrast between the two types of patients allowed us to determine if the request to make a particular type of movement with the plegic hand, at the same time as another movement with the ipsilesional hand, will have more objective impact on actual movements with the intact hand when a patient believes and experiences that their paralysed hand can still move (AHP) versus when they are aware of the hemiplegia (hemiplegic).

We also investigated the performance of two right-hemisphere patients without hemiplegia who were affected by the distinct neurological syndrome of motor neglect, which provides an intriguing contrast to AHP; indeed, motor neglect can in some respects be considered the opposite of AHP. Sometimes described as 'pseudo-hemiplegia' (Laplane and Degos, 1983) and often interpreted as the consequence of a damage to intentional motor circuits (Gold *et al*., 1994; Berti *et al*., 2007), motor neglect is characterized by underutilization of the contralesional limb in presence of normal strength, reflexes and sensibility and thus preserved potential for actual movement on the affected side. Crucially, when patients with motor neglect are asked to perform bimanual movements they only perform ipsilesional hand movements (Laplane and Degos, 1983; Punt *et al*., 2006), even though they are actually capable of moving the contralesional hand (unlike AHP cases). We predicted that in these patients the usual bimanual interference effect should not be observed for the circle/line drawing task, if such cases do not intend/plan contralesional movements in bimanual situations.

Finally, we also explored the possible presence of bimanual coupling effects in an imagery condition, in which participants were now required merely to 'imagine' that the left hand was drawing circles while the right hand was actually drawing lines (Fig. 1, 'Imagery Circles-Lines' condition). Note that for hemiplegic patients (AHP and hemiplegic) and patients with motor neglect, real movement and imagery bimanual conditions, although different in terms of the request to the patient, were comparable in the sense that these patients did not actually move their contralesional limb (could not in the case of AHP and hemiplegic, did not in practice for motor neglect, as confirmed below). Although motor imagery can show some overlapping brain activations with actual movement (Porro *et al*., 2000), this overlap is not complete. Any differences found here between the imagery conditions and the real bimanual conditions, in terms of the impact on the right hand, must presumably reflect a different level of penetration into movements by the right hand from intended/planned versus imagined movements of the left hand.

Materials and methods

Participants

Ten right-handed neurological patients with focal right brain lesions due to cerebrovascular accident were recruited as experimental subjects. Inclusion criteria were as follows: (i) for AHP and hemiplegic: presence of complete contralesional left upper limb plegia, as reported by the responsible neurologist and confirmed by a motor impairment examination carried out according to a clinical protocol (Spinazzola *et al*., 2008), with the score ranging from 0 (no paralysis) to 3 (complete paralysis, as required here). Following these criteria eight patients with complete left paralysis of the upper limb were admitted to the study (five hemiplegic and three AHP, see below); and (ii) for patients with motor neglect: absence of paresis and of any other muscle disturbances (as reported by the responsible neurologist and confirmed by direct motor impairment examination), with only a lack of spontaneous use of the contralesional hand. Following these criteria we recruited two right hemisphere brain-damaged patients with motor neglect (see below for further details). Exclusion criteria for hemiplegic, AHP and motor neglect were: (i) previous neurological or psychiatric history; and (ii) severe general cognitive impairment (assessed by Mini-Mental State Examination, Measso *et al.*, 1993).

A total of 10 right-handed healthy subjects, 5 male and 5 female, between 60 and 80 years of age (mean age; 68.5 years), were recruited as a healthy control group.

Diagnosis of anosognosia for hemiplegia

Patients were classified as having AHP based on a standard interview that explored their awareness for their motor deficits (Score 0–2; Berti *et al*., 1996). We also tested motor awareness by calculating a deviation score between patients' self-evaluation and the examiner's evaluation of the actual execution of unimanual and bimanual actions (Score 0–2; Spinazzola *et al*., 2008). As a further measure of patients' awareness we used the Visual Analogue Test for Anosognosia for motor impairment (Della Sala *et al*., 2009).

According to both tests, three out of eight patients with a complete left upper limb paralysis showed AHP. Patient AB had moderate AHP; Patients CI and EG had severe AHP. Five out of the eight patients with complete left upper limb hemiplegia were fully aware of their paralysis (Patients CG, PI, VG, PG and PL) (Table 1).

In order to study motor awareness during the execution of the bimanual tasks, a specific motor awareness self-evaluation scale was administered to all the hemiplegic patients. In this task the deviation score between the examiner's evaluation score and the patient's self-evaluation score was then calculated and taken as index of

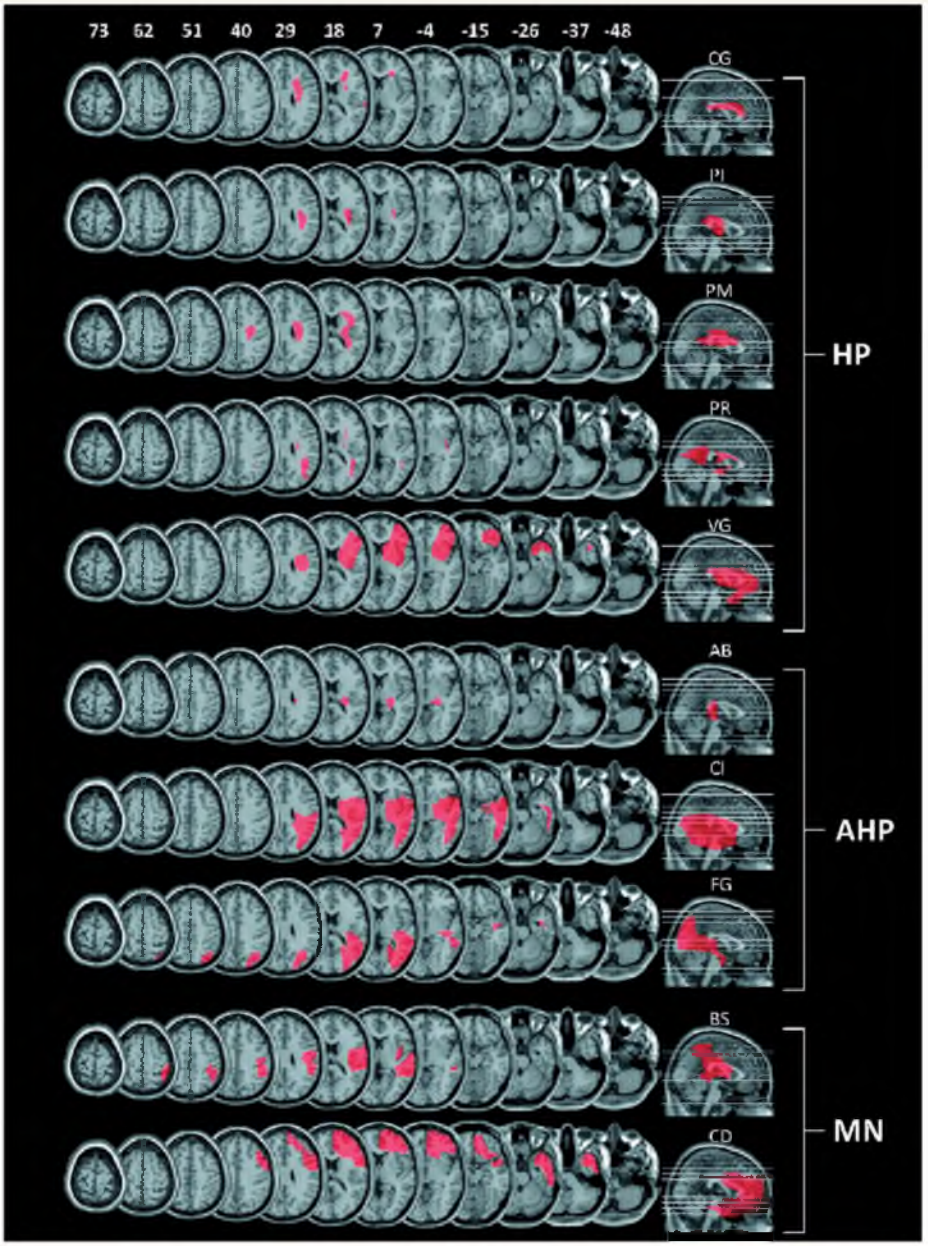

Figure 1 Patients' reconstructed lesions. Hemiplegic (HP) patients: Patient CG had right fronto-parietal cortical-subcortical lesions involving external capsule, caudate nucleus, supramarginal gyrus and frontal periventricular white matter. Patient PI had right parietal cortical-subcortical lesions involving putamen, internal and external capsule, insula and parietal periventricular white matter. Patient PM had right temporo-parieto-frontal cortical-subcortical lesions involving internal and external capsule, insula and temporo-parieto-frontal periventricular white matter. Patient PR had right temporo-parieto-frontal cortical-subcortical lesions involving middle and superior temporal pole, internal and external capule and temporo-parieto-frontal periventricular white matter. Patient VG had right fronto-parietal cortical-subcortical lesions involving middle and superior temporal pole, inferior and middle orbital gyrus, middle frontal gyrus, frontal operculum, rolandic operculum, insula, internal and external capsule, putamen, caudate nucleus, globus pallidus and fronto-parietal periventricular white matter. Patients with AHP: Patient AB had right temporo-parietal cortical-subcortical lesions involving thalamus, posterior insula and temporo-parietal periventricular white matter. Patient CI had right occipito-temporo-parieto-frontal lesions involving inferior, middle and superior temporal gyrus, angular gyrus and supramarginal gyrus, lateral premotor area 6 (sparing supplementary motor area and pre-supplementary motor area), anterior and posterior insula, precentral and postcentral gyrus, internal and external capsule, thalamus, putamen and right occipito-temporo-parieto-frontal periventricular white matter. Patient FG had right cortical-subcortical lesions involving middle and superior occipital gyrus, middle and superior temporal gyrus, angular gyrus and superior parietal lobe, posterior insula and internal capsule. Patients with motor neglect (MN): Patient BS had right temporo-parieto-frontal cortico-subcortical lesions involving inferior parietal lobe, middle and superior temporal lobe, rolandic operculum, insula, precentral gyrus, supramarginal gyrus and temporo-parietal-frontal periventricular white matter. Patient CD had right fronto-temporal cortico-subcortical lesions involving inferior, middle and superior orbital cortex, inferior, middle and superior frontal gyrus, frontal operculum, precentral gyrus, inferior, middle and superior temporal lobe, frontal periventricular white matter.

patient's unawareness during task execution. Hemiplegic patients' self-evaluation was consistent with their real motor conditions: that is, during the bimanual coupling task, hemiplegic patients were fully aware of the motor impairment in the left hand. In contrast, patients with AHP' self-evaluation was incongruent with the examiner's evaluation. All patients with AHP were completely unaware that the left hand was not moving, believing that they were successfully performing bimanual actions (even though their paralysed left limb could not move) during the drawing tasks that are illustrated in Fig 2. See Table 2 for details.

Diagnosis of motor neglect

Patients were classified as having motor neglect based on the following clinical observations (Laplane and Degos, 1983): (i) spontaneous underutilization of the contralesional upper limb and hand, despite no paralysis; (ii) non-participation or feeble participation in bimanual tasks; (iii) under- or non-participation of the contralesional hand in spontaneous gesturing when speaking; and (iv) contrast between spontaneous underutilization of the left arm and hand, versus normal movement and strength when the examiner actively encouraged the patient to use the arm. According to these criteria we recruited two patients with motor neglect without any other motor impairment (Patients BS and CD).

Table 1 Patients' AHP evaluation

Groups	AHP			Hemiplegic				
Patient	AB	CI	FG	CG	PI	VG	PG	PL
Interview[a]	1	2	2	0	0	0	0	0
Actual movement self-evaluation[b]	2	2	2	0	0	0	0	0
Visual Analogue Test for Anosognosia[c]	18	36	36	0	0	0	0	0

a Motor awareness interview scores (Berti *et al.*, 1996): 0 = no AHP; 1 = moderate AHP; 2 = severe AHP.
b Deviation score between the examiner's evaluation and the patient's self-evaluation of the actual execution of unimanual and bimanual actions: 0 = full accord in all questions (no anosognosia); 1 = disagreement in one or two questions (moderate anosognosia); 2 = disagreement in all questions (severe anosognosia) (Spinazzola *et al.*, 2008).
c Visual Analogue Test for Anosognosia scores: 6–12 = mild AHP; 12–24 = moderate AHP; 24–36 = severe AHP (Della Sala *et al.*, 2009).

Neurological/neuropsychological assessment

All patients were further assessed using standardized tests for extrapersonal neglect (Behavioural Inattention Test, Wilson *et al.*, 1987 and Bells Test, Gauthier *et al.*, 1989) and for personal neglect (Fluff Test, Cocchini *et al.*, 2001). We also evaluated visual field defects, plus tactile and proprioceptive sensory deficits. Patients' demographic characteristics and their performance on neurological/neuropsychological tests are summarized in Table 3. All participants gave informed consent for both the experiment and the video. The study was approved by the local Ethical Committee.

Brain lesions

Brain lesions, as documented by clinical CT or MRI scans, were mapped in the stereotactic space of Talairach and Tournoux using a standard MRI volume that conformed to that space as redefined by the Montreal Neurological Institute (Talairach and Tournoux, 1988). Image manipulations were performed with MRIcro software.

All hemiplegic patients (hemiplegic and AHP) had lesions mainly involving the territory of the right middle cerebral artery with subcortical damage often affecting basal ganglia and internal capsule also. It may be worth noting that in the patients with motor neglect these

Table 2 'On-Line' motor awareness evaluation

Groups	Controls	Hemiplegic patients					Patients with AHP		
Subjects	10 subjects Mean	CG	PI	VG	PG	PL	AB	CI	FG
Self-evaluation	4	0	0	0	0	0	3	4	4
Examiner evaluation	4	0	0	0	0	0	0	0	0
Deviation score	0	0	0	0	0	0	3	4	4

In the Bimanual Circles-Lines condition, at the end of each trial, participants were required to judge on a Likert scale their performance during the actual execution of bimanual movements Circles-Lines (0 = absent; 1 = poor; 2 = medium; 3 = good; 4 = very good) with respect to both hands. Here we only show the score relating to the left hand (the right hand score was 4 in all patients/controls). The examiner evaluated the subject's bimanual performance on the same Likert scale. We calculated the deviation score between the examiner's evaluation and the patient's self-evaluation. Note that strong deviation only arose for the AHP Patients AB, CI and FG, due to their false belief that they moved the paralysed hand when bimanual movements were requested in the drawing task.

Figure 2 Circles-Lines bimanual motor task. Experimental conditions: Unimanual-Line (U-L), Bimanual Circle-Line (B-CL) and Imagery Circle-Line (I-CL).

structures were spared, confirming the absence of lesional patterns that typically induce true hemiplegia rather than spontaneous underuse. Figure 1 illustrates lesions reconstructions of the patients as documented by clinical CT or MRI scans, although we note that any definitive statement on anatomy for the different groups would require larger samples, beyond the focus of the present study which concerned the behavioral outcome for the bimanual drawing task.

Circles-lines bimanual motor task

While blindfolded each participant was asked to perform unimanual or bimanual movements in different conditions, which required continuous drawing of vertical lines and/or circles, without interruption, for 12 s on each trial. Movement trajectories were automatically recorded by a tablet PC for the right non-paralysed hand. Patients were always asked to draw vertical lines with the right hand, and only right hand movements were registered on the tablet. When bimanual movements were requested, the left hand had to draw on a sheet of paper. For each trial an ovalization index was calculated as the standard deviation of the right hand trajectory from an absolute vertical line (see Supplementary material for its computation). Each participant sat in front of a table on which the tablet PC lay, positioned to the right of the participant's sagittal midline.

The experimental conditions were as follows (Fig. 2): (i) Unimanual Lines: subjects were asked to draw vertical lines with the right hand; (ii) Bimanual Circles-Lines: subjects were asked to simultaneously draw vertical lines with the right hand and circles with the left hand; and (iii) Imagery Circles-Lines: subjects were asked to draw lines with the right hand while imagining that they were concurrently drawing circles with the left hand.

There were six trials for each condition, for a total of 18 trials, presented accordingly to the following balanced sequence: three Unimanual Lines; three Bimanual Circles-Lines; three Imagery Circles-Lines; three Imagery Circles-Lines; three Bimanual Circles-Lines; and three Unimanual Lines. Because it might be difficult to imagine a particular movement never tried before, the imagery condition always followed the real bimanual condition in all participants. The different types of patients were thus all comparable in this respect.

Results

The expected bimanual coupling effect (Franz *et al*., 1991) should take the form of an increase in the ovalization index for the right-hand trajectory in the Bimanual Circles-Lines condition with respect to the baseline unilateral-lines condition. Illustrative examples of right hand trajectories for the Bimanual Circles-Lines condition are shown in Fig. 3. An example of AHP performance during the task is shown in Supplementary Video 3.

Figure 4 shows bar-plots illustrating mean ovalization index for each patient of each type, and for the normal group, with separate bars shown for the baseline Unimanual Lines condition, the critical Bimanual Circle-Line condition, plus the imagery condition. The key result is that when a real circling movement was requested for the left hand, ovalization for the right hand was evident for healthy controls and patients with AHP, but not for hemiplegic patients or patients with motor neglect. Note the increased ovalization index for patients with AHP and normal controls, but not for hemiplegic or patients with motor neglect, in the real-bimanual condition relative to the unilateral or imagery condition.

We first compared the normal, AHP and hemiplegic groups by factorial ANOVA, before moving on to consider the two patients with motor neglect as single-cases. A Shapiro–Wilk's test confirmed no significant ($P > 0.5$, not significant) deviation from normality for the normal AHP, and hemiplegic groups, so we proceeded to a 3×3 mixed ANOVA on the ovalization index data with Group (Controls, AHP, Hemiplegic patients) as a between-subjects factor and Condition (Unimanual Lines, Bimanual Circles-Lines, Imagery Circles-Lines) as a within-subject factor.

Table 3 Patients' demographic characteristics and neuropsychological assessment results

Group	AHP			Motor neglect		Hemiplegic				
Patient	AB	CI	FG	BS	CD	CG	PI	VG	PR	PM
Age (years)	66	84	72	76	67	62	70	79	68	71
Education (years)	8	18	5	3	10	8	5	13	8	13
Days from onset	62	32	28	27	65	36	60	31	25	30
Hemiplegia u.l.–l.l. (0 = no hemiplegic; 3 = complete hemiplegic)	3–2	3–3	3–2	0	0	3–3	3–2	3–3	3–1	3–3
MMSE (cut-off $\geqslant$ 24/30)	29/30	28/30	26/30	24/30	26/30	28/30	27/30	24/30	28/30	26/30
BIT conventional and behavioural subtests (cut-off $\geqslant$ 129/146; $\geqslant$ 67/81)	103/146 65/81	13/146 8/41	101/146 64/81	43/146 26/81	112/146 60/81	115/146 65/81	92/146 15/81	125/146 37/81	131/146 79/81	121/146 52/81
Bells (cut-off omissions l – r < 3)	3	3	9	10	15	11	8	3	2	12
Fluff (cut-off omissions l $\leqslant$ 2)	3	8	1	4	0	14	0	4	1	3
Hemianesthesia tactile;	0–0	3–3	1–1	0–0	0–0	2–2	1–0	2–2	0–0	2–2
proprioceptive, u.l.– l. L. (0 = no deficit; 1 = extinction; 2 = middle hae; 3 = severe hae)	0–0	3–3	0–0	0–0	0–0	2–2	00	2–1	0–0	1–0
Visual field superior–inferior quadrant (0 = no deficit; 1 = extinction; 2 = middle hao; 3 = severe hao)	0–0	3–3	1–1	2–2	0–0	1–1	3–2	0–0	0–0	1–1

BIT = Behavioural Inattention Test; MMSE = Mini-Mental State Examination.

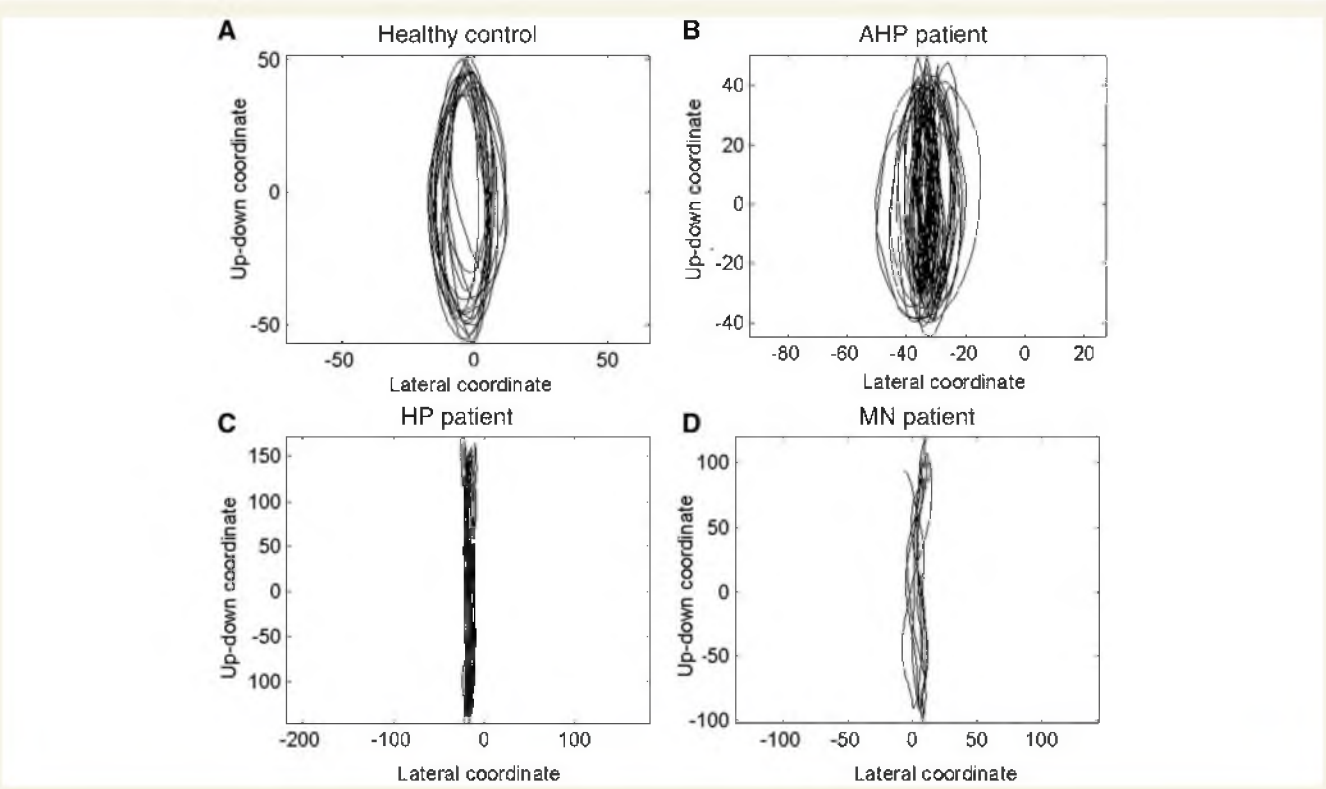

Figure 3 Examples of subjects' right hand trajectory in Bimanual Circle-Line condition. Note the increased ovalization for healthy controls (**A**) and for patients with AHP (**B**), but not for hemiplegic (HP; **C**) or patients with motor neglect (MN; **D**).

The ANOVA found main effects of Group [$F(3, 16) = 5.838$; $P = 0.007$] and Condition [$F(2, 32) = 6.012$; $P = 0.006$], but more importantly an interaction [$F(6, 32) = 2.799$; $P = 0.02$]. This interaction arose because the bimanual coupling effect was evident only in healthy controls and patients with AHP, not for hemiplegic patients; and only in the actual motor-execution condition (Bimanual Circles-Lines) for the former two groups. Duncan *post hoc* comparisons confirmed a significant difference between Bimanual Circles-Lines and Unimanual Lines (the critical coupling effect) in healthy controls ($P = 0.001$) and in patients with AHP ($P = 0.004$), but not for hemiplegic patients ($P = 0.9$). We found no significant difference between Unimanual Lines and Imagery Circles-Lines conditions (Controls: $P = 0.2$; AHP: $P = 0.5$; Hemiplegic: $P = 0.8$) in any of the groups, indicating no imagery effect. Duncan tests further confirmed that for the critical Bimanual Circles-Lines condition there was a significant difference between AHP and Hemiplegic groups ($P = 0.001$) as well as between Controls and Hemiplegic ($P = 0.001$). The lack of any such difference between AHP and Controls ($P = 0.8$) indicates that the coupling effect found in patients with AHP for the Bimanual Circles-Lines condition is comparable to that found in normal subjects. For full descriptive statistics see Supplementary Table 1.

Given the small number of patients with motor neglect, we did not include them as a group in the analysis above. Instead we performed one-way ANOVAs with ovalization index as the dependent variable and the three-level factor of Condition (Unimanual Lines, Bimanual Circles-Lines, Imagery Circles-Lines) within each patient with motor neglect, using trials for the random error term. Neither of the patients with motor neglect showed a significant effect of Condition [Patient CD: $F(2, 15) = 1.001$; $P = 0.4$; Patient BS: $F(2, 15) = 0.560$; $P = 0.6$], confirming the absence of any coupling effect in them.

For completeness, in order to verify the presence/absence of the coupling effect within each single patient from the other groups we performed ANOVAs with ovalization index as the dependent variable and the three-level factor of Condition (Unimanual Lines, Bimanual Circles-Lines, Imagery Circles-Lines), for each hemiplegic and AHP patient.

Single patients with anosognosia for hemiplegia

For Patient AB [$F(2, 15) = 53.128$; $P = 0.00001$], *post hoc* analysis confirmed the significant difference between Unimanual Lines and Bimanual Circles-Lines ($P = 0.0001$) and between Bimanual Circles-Lines versus Imagery Circles-Lines ($P = 0.0002$) with no difference between Unimanual Lines and Imagery Circles-Lines condition ($P = 0.4$).

For Patient CI [$F(2, 15) = 14.964$; $P = 0.0003$], *post hoc* analysis again confirmed the difference between Unimanual Lines versus Bimanual Circles-Lines ($P = 0.0002$) and Bimanual Circles-Lines versus Imagery Circles-Lines ($P = 0.0034$). The difference between Unimanual Lines and Imagery Circles-Lines condition was not significant ($P = 0.06$).

For Patient FG [$F(2, 15) = 9.123$, $P = 0.0026$], *post hoc* analysis again confirmed a significant difference between Unimanual

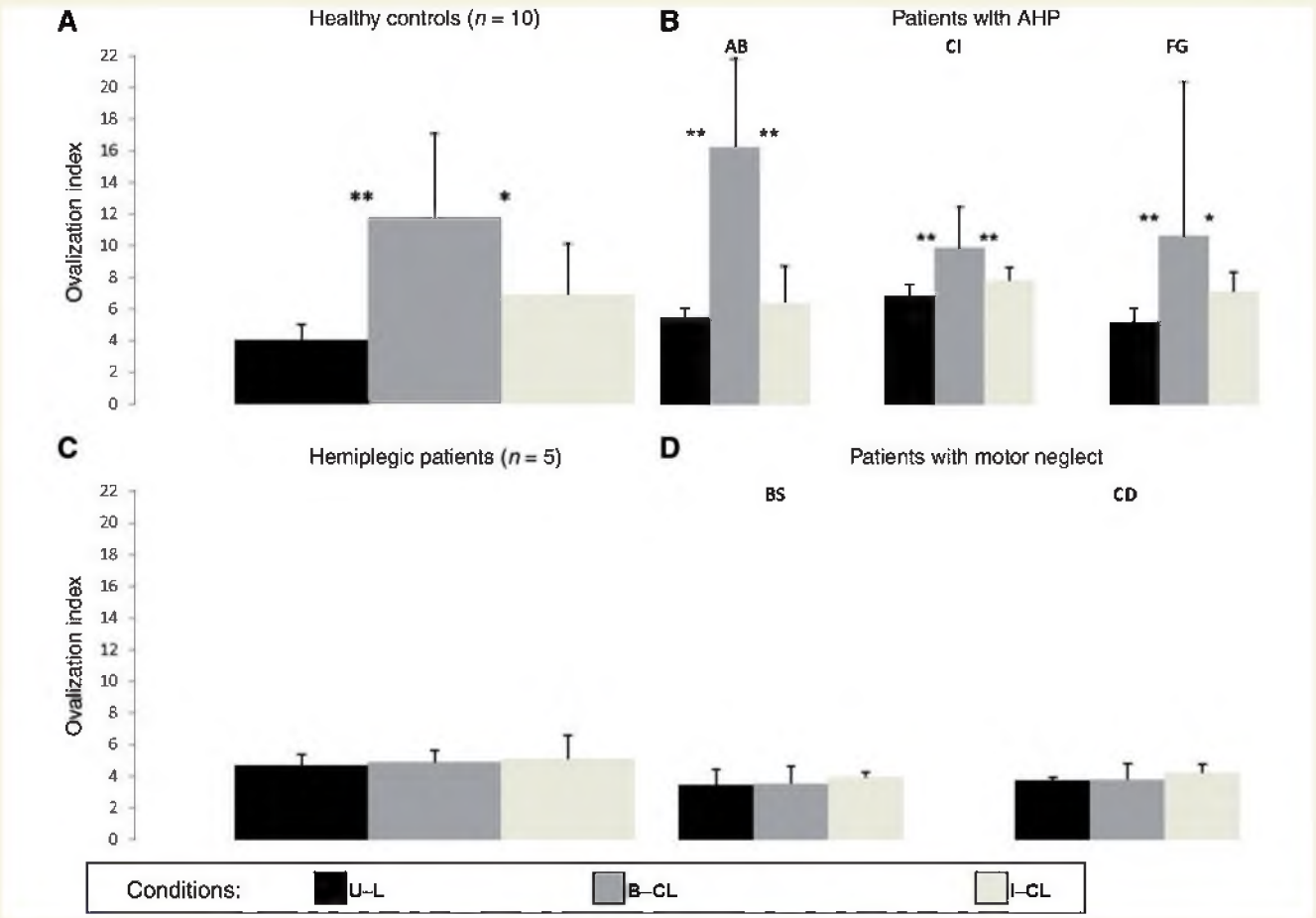

Figure 4 Statistical results. (**A–D**) For each patient/group, results of ANOVA with ovalization index values for the right hand as dependent variable and three-level factor of Condition: Unimanual-Line (U-L), Bimanual Circle-Line (B-CL) and Imagery Circle-Line (I-CL). $^{*}P < 0.05$; $^{**}P < 0.005$.

Lines versus Bimanual Circles-Lines ($P = 0.0022$) and Bimanual Circles-Lines versus Imagery Circles-Lines ($P = 0.0159$) but not between Unimanual Lines versus Imagery Circles-Lines ($P = 0.1$).

To summarize, each patient with AHP showed a clear, individually significant coupling effect in the actual motor condition, whereas the coupling effect was not significant in the imagery condition.

Single hemiplegic patients

None of the hemiplegic patients showed a coupling effect, neither in the actual motor nor in the imagery condition, leading to no significant impact of condition on ovalization index in the one-way ANOVAs. Patient CG: $F(2, 15) = 0.126$; $P = 0.9$; Patient PI: $F(2, 15) = 0.373$; $P = 0.7$; Patient PM: $F(2, 15) = 2.628$; $P = 0.1$; Patient PR: $F(2, 15) = 1.465$; $P = 0.2$; Patient VG: $F(2, 15) = 1.582$; $P = 0.2$.

Discussion

The principal aim of the present experiment was to test whether patients with AHP, with complete left hemiplegia but the subjective illusion that they can still move their plegic limb, may have intact motor intentionality/planning for the affected limb, as would be implied if a request to move the contralesional hand in a particular way impacted on objective performance by the intact right hand in a bimanual task. We adapted the bimanual task from Franz *et al*. (1991), who reported bimanual coupling effects in normal subjects when one hand had to draw a circle and the other a line, with the latter hand taking on an 'oval' trajectory due to interference from the circle programme for the other hand. The results confirmed our hypothesis by showing that patients with AHP had a clear coupling effect in the bimanual condition when requested to actually perform bimanual movement. This coupling effect was comparable, despite the plegic left hand, to that of healthy controls and was present in each AHP case individually. This outcome clearly demonstrates that, despite their paralysis, patients with AHP are still able to generate representations of the desired motor states that are sufficient to lead to the bimanual interference effect.

Considering the other neurological/neuropsychological symptoms associated with AHP in the present cases, we can confirm that extrapersonal neglect, personal neglect, sensory disorders and intellectual deficits, although present in different combinations in different patients, appear neither to be sufficient (they are present

also in the other groups of patients) nor necessary (they are not all present in all patients with AHP) to cause AHP and the present associated bimanual coupling results, at least in the patients we selected (Table 3). However, there is one neuropsychological observation that may be noteworthy. Two out of the three patients with AHP had personal neglect in the Fluff test and one of them, Patient CI who had the worst score in the personal neglect test, also had a severe tactile/proprioceptive deficit. That is, Patient CI also had severe impairments in body representation on the same side as AHP. Although a common finding in the literature on AHP, a somewhat counterintuitive aspect here is that a patient with such an impairment of contralesional body representation is evidently still able to intend/plan motor action with the affected side, at least as indicated by the objective bimanual coupling effect observed for the intact hand in our study. This may be in keeping with the idea that motors intentions/plans may involve predictive aspects (as in 'forward models' of motor cognition; Blakemore *et al*., 2002), separate from sensory feedback for the actual spatial position of the body, which was clearly deficient in Case CI.

Unlike AHP and normal control subjects, hemiplegic patients without anosognosia did not show any coupling effect in the bimanual condition. This outcome in hemiplegic patients is not trivial. In principle, it might be expected that hemiplegic patients, with apparently normal motor awareness (albeit for hemiplegia) and no evident sign of damage to brain areas traditionally related to motor planning, could have shown a coupling effect similar to that found in healthy subjects. But the defining difference between hemiplegic and AHP patients is that only the hemiplegic cases are aware of their hemiplagia, unlike AHP. As a result they may not attempt to move the plegic limb (or may not program this internally) even when requested. As a consequence the distal effect of such plans on the intact hand (the coupling effect) is no longer observed. Moreover, all hemiplegic patients of the present study were tested in the chronic phase, by when their motor systems may have 'learned' the paralysis. In accord with our data in hemiplegic patients, Franz and Ramachandran (1998) found neither phantom experiences nor coupling effects in amputees who, long before the amputation, had been paralysed, suggesting that when the system has learned the paralysis, then movement programming no longer arises for the paralysed limb.

Motor neglect patients, as we had predicted, did not show any coupling effect, unlike patients with AHP or normal controls. This was the same outcome as for hemiplegic cases, even though patients with motor neglect differ in being physically capable of moving the contralesional limb. We had predicted an absence of bimanual coupling in motor neglect because such patients typically do not use that contralesional hand spontaneously, nor in bimanual tasks, which are often attributed to a lack of intention/planning for the affected hand (Laplane and Degos, 1983; Gold *et al*., 1994; Berti *et al*., 2007). The motor neglect cases provide an interesting contrast to the cases with AHP, with the former non-plegic but apparently lacking intention/planning, whereas the latter are plegic but evidently still maintain intentions/plans for the affected hand, at least sufficiently to induce an objective impact on the intact hand as found here via the bimanual coupling effect. AHP cases are of course by definition unaware of their paralysis. It might be interesting in future work to examine whether or not patients with motor neglect have insight into their under-use of the (non-plegic) contralesional hand. We did not implement the standard measures for AHP in the motor neglect cases here, because those standard measures all relate to hemiplegia, which was not present in the motor neglect cases by definition. Different measures would thus be required to assess any self-insight concerning motor neglect.

Although many studies indicate a close link between motor imagery and motor planning/execution (Jeannerod and Frak, 1999), we did not observe a bimanual coupling effect here for the imagery condition (Imagery Circles-Lines) of our experiment in any of the groups (Fig. 4). One possibility is that motor imagery and motor planning/execution, while sharing similar brain circuits, rely on different activation strengths. Functional MRI studies (Porro *et al*., 2000) have shown that activation of the motor cortices reported during explicit motor imagery can typically be much less (e.g. ~30%) of the level observed for real movements. This might explain why the bimanual coupling effect was more evident here when real rather than imaginary movements of the left hand were requested. But the most important point for present purposes is that the lack of bimanual coupling in the imagery condition (for all groups alike) indicates that the effects found in the actual bimanual condition (Bimanual Circles-Lines), for both normal and AHP, cannot be merely ascribed to imagery of the requested movement. Evidently the AHP cases went further than mere imagery in their motor intentions/planning, when real circle movements of the left hand were requested, even though they could not move that plegic hand. Of course the patients with AHP actually believe that they can move that hand at will, despite their paresis.

It is interesting to consider the possible causal role of patients with AHP' pathological belief of still being able to move the paralysed hand for the objective impact we observed here on the right hand. Cocchini *et al*. (2010) have argued that AHP can be heterogeneous, with some patients having implicit knowledge of their deficit (Nardone et *al*., 2007; Fotopoulou *et al*., 2010). Cocchini *et al*. (2010) asked their subjects to perform a series of bimanual tasks, which are usually accomplished using two hands, but could also be performed using one hand only. Although most patients with AHP tend to accomplish these tasks as if they could use both hands, some patients approached the task using one hand, thereby exhibiting some implicit knowledge of their motor deficit. Among the battery of tests used here for evaluation of AHP (Table 1), one involved requests to perform everyday bimanual actions, similarly to the bimanual motor battery proposed by Cocchini *et al*. (2010). All three patients with AHP in the present study, who had explicit AHP in conventional tests, also showed implicit AHP on such everyday bimanual actions. That is they planned bimanual movements as if they could use both hands without adopting any compensatory unimanual strategy (Supplementary Video 4). It would be interesting to study a larger sample of AHP cases in future with the paradigm introduced here, to see if the bimanual coupling effect depends on the presence/absence of implicit knowledge for the hemiplegia, as revealed by the bimanual tasks of Cocchini *et al*. (2010).

Our results in the coupling experiment may potentially relate to another AHP study by Fotopoulou *et al*. (2008) of a situation where, by using a realistic prosthetic hand, they could generate

false visual feedback of patients' limb movements. They examined whether patients' ability to detect presence or absence of movement based on visual evidence varied when they had actually planned the movements or not. They found that patients with AHP were more ready to claim that their plegic hand moved when asked to move that hand themselves (internally generated movement) than when told that the experimenter would passively move their hand (externally generated movement). These results were interpreted as due to the possible predominance, in patients with AHP, of motor intention over sensory feedback in the construction of the pathological belief that their plegic limb can move.

Franz and Ramachandran (1998) studied amputee patients with vivid subjective experience of moving their 'phantom' limb, finding a bimanual coupling effect similar to that observed here in our patients with AHP. On the basis of such results, Frith *et al.* (2000) proposed that motor representations in phantom limb and patients with AHP may be based more on forward predictive streams of motor command than on sensory feedback (Berti and Pia, 2006). But a crucial difference between amputees and patients with AHP is that the latter have brain damage preventing the patients from realizing that their subjective experience is non-veridical. Although some amputees can intentionally manipulate their phantom, all are aware, in the absence of brain damage that actual movements do not occur.

Anatomically, AHP has been related to lesions mainly involving pre-motor and insular areas (Berti *et al.*, 2005; Karnath *et al.*, 2005; Fotopoulou *et al.*, 2010; Vocat *et al.*, 2010), thought to provide the neural basis of a complex circuit related to comparator components of the motor system; whereas motor-intentional processes are thought to involve brain centres localized in pre-frontal areas and the inferior parietal lobule (Libet *et al.*, 1983; Haggard and Magno, 1999; Lau *et al.*, 2004; Desmurget *et al.*, 2009; Fried *et al.*, 2011). It may be noteworthy that our patients with AHP had lesions affecting some of the structures in the proposed comparator system (AHP Patient CI: both pre-motor and insular areas; AHP, Patients AB and FG only insular areas), sparing the frontal aspect of the motor intentional system; whereas patients with motor neglect had lesions mostly involving the latter (motor neglect Patient CD: prefrontal areas; motor neglect Patient BS: inferior parietal areas). But larger anatomical samples are clearly required to clarify the neural bases of the dissociation between AHP and motor neglect.

It is interesting to note that all three patients with AHP here had lesions affecting the posterior part of the insula and for one of the three (Patient CI) also the anterior part. These lesional aspects apparently converge with the Berti *et al.* (2005) and Karnath *et al.* (2005) findings, who reported that the insula can be critically affected in patients with AHP. In particular, Karnath *et al.* (2005) found that in their sample, the posterior part of the insula was the area most frequently affected in AHP. However, using a different statistical mapping method, Vocat *et al.* (2010) found a greater involvement of the anterior part of the insula. Interestingly, Fotopoulou *et al.* (2010) observed, in five patients with explicit (but not implicit) AHP, that their lesions affected the anterior (not posterior) part of the insula, with sparing of premotor cortex. In this latter study, the premotor cortex was affected only in the patient who showed implicit AHP.

Finally, two of the patients with AHP in our study had extensive lesions affecting also the fronto-temporo-parietal cortices (Patient CI) and the parieto-temporal cortices (Patient FG) and were in the chronic phase of the illness. This may accord with recent suggestions of more extensive lesions, involving premotor and parieto-temporal cortices, in chronic than in patients with acute AHP (Vocat *et al.*, 2010).

We take the preserved bimanual coupling in the AHP cases to indicate that motor intentions/plans are sufficiently preserved in them for the paralysed hand to produce the observed objective bimanual coupling effect for the intact hand. But the broad concept of motor 'intentions/plans' for the paralysed hand may ultimately need further unpacking into several possible distinct internal processes (potentially including motor preparation, detailed motor programming, efference copies, motor attention, or explicit awareness of motor goals) in future extensions of the present work. It might be revealing also to perform neuroimaging in all the different types of participant studied here (normal, AHP, hemiplegic and motor neglect) to contrast the activations found for the critical bimanual versus unimanual conditions.

Conclusion

Our results indicate that bimanual spatial coupling, as found in normal subjects but not present in patients with motor neglect nor in hemiplegia without anosognosia, can be preserved in anosognosic hemiplegic patients, despite the absence of actual movements by their paralysed left hand. The anosognosic patients can evidently still generate sufficient motor intentions/plans for the affected hand (that they believe subjectively to move), for these to impact on objective movements for the intact right hand just as if a real left-hand movement had arisen. Although the anosognosic patients are incorrect to believe that their left hand can still move, it is evident that internal motor representations for that left hand can still operate in a different way to that found for purely hemiplegic patients, or for cases with motor neglect. It must be noted that our results do not directly demonstrate that the motor signal related to the activation of the intention programming system is the basis of the patients with AHP' action awareness, although they are consistent with this view. The key innovation of our data is in providing objective performance evidence for the existence of such a signal that could contribute to awareness. Further research should directly address the issue of the causal status of phenomenal experience.

Finally, the demonstration of preserved motor intentions/plans may not explain all features of anosognosia. For example, it remains unclear why anosognosic patients typically insist not only that they can still move the hemiplegic limb, but also that they can still successfully complete everyday tasks that they are manifestly incapable of and fail on repeatedly. Future studies should examine whether such phenomena involve concomitant emotional factors, or whether preserved motor intentions/plans, when combined with an inability to update the actual status of the body, may also be sufficient to explain such symptoms.

Acknowledgements

We are grateful to patients for their cooperation and their patience and to Gabriella Tocchi and Sara Bochicchio for their help during testing. We are indebted to Vittorio Gallese for his helpful comments on the first draft of the paper.

Funding

This study was funded by a Compagnia di San Paolo grant and a MIUR-PRIN grant (to A.B.).

References

Babinski J. Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie). Rev Neurol 1914; 27: 845–48.

Adair JC, Gilmore RL, Fennell EB, Gold M, Heilman KM. Anosognosia during intracarotid barbiturate anesthésia: unawareness or amnesia for weakness. Neurology 1995; 45: 241–3.

Anton G. Über herderkrankungen des gehirnes, welche vom patienten selbst nicht wahregenommen werden. Wien Klin Wochenschr. Wochenschrift 1898; 11: 227–9.

Anton G. Über die Selbstwahrnehmung der herderkrankungen des gehirnes durch den kranken bei rindenblindheit und rindentaubheit. Arch Psychiatr Nervenkr 1899; 32: 86–127.

Berti A, Pia L. Understanding motor awareness through normal and pathological behavior. Curr Dir Psychol Sci 2006; 15: 245–50.

Berti A, Làdavas E, Della Corte M. Anosognosia for hemiplegia, neglect dyslexia, and drawing neglect: clinical findings and theoretical considerations. J Int Neuropsychol Soc 1996; 2: 426–40.

Berti A, Spinazzola L, Pia L, Rabuffetti M. Motor awareness and motor intention in anosognosia for hemiplegia. In: Haggard P, Rossetti Y, Kawato M, editors. XXII Attention and Performance International Symposium, Sensorimotor Foundations of Higher Cognition. New York: Oxford University Press; 2007. p. 163–81.

Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, et al. Shared cortical anatomy for motor awareness and motor control. Science 2005; 309: 488–91.

Bisiach E, Geminiani G. Anosognosia related to hemiplegia and hemianopia. In: Prigatano G, Schacter DL, editors. Awareness of deficit after brain injury. Clinical and theoretical issues. New York: Oxford Universitary Press; 1991. p. 17–39.

Blakemore SJ, Wolpert DM, Frith CD. Abnormalities in the awareness of action. Trends Cogn Sci 2002; 6: 237–42.

Bottini G, Paulesu E, Gandola M, Pia L, Invernizzi P, Berti A. Anosognosia for hemiplegia and models of motor control: insights from lesional data. In: Prigatano G, editor. Advances in the Study of Anosognosia. New York: Oxford University Press; 2010. p. 17–38.

Cocchini G, Beschin N, Jehkonen M. The Fluff Test: A simple task to assess body representation neglect. Neuropsychol Rehabil 2001; 11: 17–31.

Cocchini G, Beschin N, Fotopoulou A, Della Sala S. Explicit and implicit anosognosia or upper limb motor impairment. Neuropsychologia 2010; 48: 1489–94.

Colsett HB. Anosognosia and body representations forty years later. Cortex 2005; 41: 263–70.

Della Sala S, Cocchini G, Beschin N, Cameron A. Vatam: a new method to assess anosognosia for upper and lower limbs in left-and right brain damaged patients. Clin Neuropsychol 2009; 11: 1–22.

Desmurget M, Reilly KT, Richard N, Szathmari A, Mottolese C, Sirigu A. Movement intention after parietal cortex stimulation in humans. Science 2009; 324: 811–3.

Feinberg TE. Anosognosia and confabulation. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. New York: McGraw-Hill; 1997. p. 369–90.

Fotopoulou A, Tsakiris M, Haggard P, Vagopoulou A, Rudd A, Kopelman M. The role of motor intention in motor awareness: an experimental study on anosognosia for hemiplegia. Brain 2008; 131: 3432–42.

Fotopoulou A, Pernigo S, Maeda R, Rudd A, Kopelman MA. Implicit awareness in anosognosia for hemiplegia: unconscious interference without conscious re-representation. Brain 2010; 133: 3564–77.

Franz EA, Ramachandran VS. Bimanual coupling in amputees with phantom limbs. Nat Neurosci 1998; 1: 443–44.

Franz EA, Zelaznik HN, Mccabe G. Spatial topological constraints in a bimanual task. Acta Psychol 1991; 77: 137–51.

Fried I, Mukamel R, Kreiman G. Internally generated preactivation of single neurons in human medial prefrontal cortex predicts volition. Neuron 2011; 69: 548–62.

Frith CD, Blakemore SJ, Wolpert DM. Abnormalities in the awareness and control of action. Philos Trans R Soc Lond B Biol Sci 2000; 355: 1771–88.

Gauthier L, Dehaut F, Joanette Y. The Bells test: A quantitative and qualitative test for visual neglect. Int J Clin Neuropsychol 1989; 11: 49–54.

Gialanella B, Mattioli F, Rocchi S, Ferlucci C. Verbal intelligence in Neglect: the role of anosognosia for hemiplegia. Eur J Phys Rehabil Med 2009; 45: 363–8.

Gold G, Adair JC, Jacobs DH, Heilman KM. Anosognosia for hemiplegia: an electrophysiologic investigation of the feed-forward hypothesis. Neurology 1994; 44: 1804–08.

Haggard P. Conscious intention and motor cognition. Trend Cogn Sci 2005; 9: 290–5.

Haggard P, Magno E. Localising awareness of action with Transcranical magnetic stimulation. Exp Brain Res 1999; 127: 102–7.

Heilman KM. Anosognosia: possible neuropsychological mechanisms. In: Prigatano G, Schacter DL, editors. Awareness of deficit after brain injury. Clinical and theoretical issues. New York: Oxford University Press; 1991. p. 53–62.

Heilman KM, Barrett AM, Adair JC. Possible mechanisms of anosognosia: a defect in self-awareness. Philos Trans R Soc Lond B Biol Sci 1998; 353: 1903–9.

Hildebrandt H, Zieger A. Unconscious activation of motor responses in a hemiplegic patient with anosognosia and neglect. Eur Arch Psychiatry Clin Neurosci 1995; 246: 53–9.

Jeannerod M, Frak V. Mental imaging of motor activity in humans. Curr Opin Neurobiol 1999; 9: 735–9.

Jenkinson M, Edelstyn NMJ, Ellis SJ. Imagining the impossible: motor representations in anosognosia for hemiplegia. Neuropsychologia 2009; 47: 481–88.

Jenkinson P, Fotopoulou A. Motor awareness in anosognosia for hemiplegia: experiments at last!. Exp Brain Res 2010; 204: 295–304.

Karnath HO, Baier B, Nagle T. Awareness of the functioning of one's own limbs mediated by the insular cortex? J Neurosci 2005; 25: 7134–8.

Laplane D, Degos JD. Motor neglect. J Neurol Neurosurg Psychiatry 1983; 46: 152–58.

Lau HC, Rogers RD, Haggard P, Passingham RE. Attention to intention. Science 2004; 303: 1208–10.

Levine DN, Calvanio R, Rinn WE. The pathogenesis of anosognosia for hemiplegia. Neurology 1991; 41: 1770–81.

Libet B, Gleason CA, Wright EW, Pearl DK. Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential).

The unconscious initiation of a freely voluntary act. Brain 1983; 106: 623–42.

Marcel AJ, Tegnér R, Nimmo-Smith I. Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. Cortex 2004; 40: 19–40.

Measso G, Cavarzeran F, Zappala G, Lebowitz BD, Crook TH, Pirozzolo FJ, et al. The Mini-Mental State Examination: Normative study of an Italian random sample. Dev Neuropsychol 1993; 9: 77–85.

Nardone IB, Ward R, Fotopoulou A, Turnbull OH. Attention and emotion in anosognosia: evidence of implicit awareness and repression? Neurocase 2007; 13: 438–45.

Orfei MD, Robinson RG, Prigatano GP, Starkstein S, Rusch N, Bria P, et al. G.Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a systematic review of the literature. Brain 2007; 130: 3075–90.

Pia L, Neppi-Mòdona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. Cortex 2004; 40: 367–77.

Pick A. Beitrage zur Pathologie und Pathologische Anatomie des Zntralnervensystems mit Bemerkungen zur normalen Anatomie desselben. Berlin: Karger; 1898. p. 168–85.

Porro CA, Cettolo V, Francescato MP, Baraldi P. Ipsilateral involvement of primary motor cortex during motorimagery. Eur J Neurosci 2000; 12: 3059–63.

Punt TD, Riddoch MJ. Motor neglect: Implications for movement and rehabilitation following stroke. Disabil Rehabilit 2006; 28: 857–64.

Spalletta G, Serra L, Fadda L, Ripa A, Bria P, Caltagirone C. Unawareness of motor impairment and emotions in right hemispheric stroke: a preliminary investigation. Int J Geriatr Psychiatry 2007; 22: 1241–6.

Spinazzola L, Pia L, Folegatti A, Marchetti C, Berti A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. Neuropsychologia 2008; 46: 915–26.

Talairach J, Tournoux L. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system — an approach to cerebral imaging. New York: Thieme; 1988.

Vallar G, Bottini G, Sterzi R. Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemiinattention: is there a relationship? Prog Brain Res 2003; 142: 289–301.

Vocat R, Staub F, Stroppini T, Vuilleumier P. Anosognosia for hemiplegia: a clinical-anatomical prospective study. Brain 2010; 133: 3578–97.

Vuilleumier P. Anosognosia. In: Bogousslavsky J, Cummings JL, editors. Behavior and mood disorders in focal brain lesions. Cambridge: Cambridge University Press; 2000. p. 465–519.

Vuilleumier P. Anosognosia: the neurology of beliefs and uncertainties. Cortex 2004; 40: 9–17.

Weinstein EA, Kahn RL. The syndrome of anosognosia. AMA Arch Neurol Psychiatry 1950; 64: 772–91.

Weinstein EA, Kahn RL. Denial of illness. Symbolic and physiological aspects. Springfield, Illinois, USA: Charles C. Thomas publisher; 1955.

Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. Science 1995; 269: 1880–82.

Wilson B, Cockburn J, Halligan P. Development of a behavioral test of visuospatial neglect. Arch Phys Med Rehabil 1987; 68: 98–102.

Zingerle H. Über Störungen der Wahrnehmung des eigenen Körpers bei organischen Gehirnerkrankungen. Monatsschr Psychiatr Neurol 1913; 34: 13–36.