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Anosognosia for hemiplegia: a clinical-anatomical prospective study

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Anosognosia for hemiplegia is a common and striking disorder following stroke. Because it is typically transient and variable, it remains poorly understood and has rarely been investigated at different times in a systematic manner. Our study evaluated a prospective cohort of 58 patients with right-hemisphere stroke and significant motor deficit of the left hemibody, who were examined using a comprehensive neuropsychological battery at 3 days (hyperacute), 1 week (subacute) and 6 months (chronic) after stroke onset. Anosognosia for hemiplegia was frequent in the hyperacute phase (32%), but reduced by almost half 1 week later (18%) and only rarely seen at 6 months (5%). Anosognosia for hemiplegia was correlated with the severity of several other deficits, most notably losses in proprioception, extrapersonal spatial neglect and disorientation. While multiple regression analyses highlighted proprioceptive loss as the most determinant factor for the hyperacute period, and visuospatial neglect and disorientation as more determinant for the subacute phase, patients with both proprioceptive loss and neglect had significantly higher incidence of anosognosia for hemiplegia than those with only one deficit or no deficits (although a few double dissociations were observed). Personal neglect and frontal lobe tests showed no significant relation with anosognosia for hemiplegia, nor did psychological traits such as optimism and mood. Moreover, anosognosia for neglect and prediction of performance in non-motor tasks were unrelated to anosognosia for hemiplegia, suggesting distinct monitoring mechanisms for each of these domains. Finally, by using a voxel-based statistical mapping method to identify lesions associated with a greater severity of anosognosia, we found that damage to the insula (particularly its anterior part) and adjacent subcortical structures was determinant for anosognosia for hemiplegia in the hyperacute period, while additional lesions in the premotor cortex, cingulate gyrus, parietotemporal junction and medial temporal structures (hippocampus and amygdala) were associated with the persistence of anosognosia for hemiplegia in the subacute phase. Taken together, these results suggest that anosognosia for hemiplegia is likely to reflect a multi-component disorder due to lesions affecting a distributed set of brain regions, which can lead to several co-existing deficits in sensation, attention, interoceptive bodily representations, motor programming, error monitoring, memory and even affective processing, possibly with different combinations in different patients.

Keywords: anosognosia; consciousness; hemiparesis

Abbreviation: VLSM = voxel-based lesion-symptom mapping

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Introduction

General background

Anosognosia (a: without; noso: disease; gnosia: knowledge) refers to a lack of awareness of motor, visual or cognitive impairments in patients with neurological disease (Berti *et al.*, 1996). This striking phenomenon occurs in various conditions such as hemiplegia, hemianopia, cortical blindness, neglect, prosopagnosia, amnesia, aphasia and dementia (Bogousslavsky and Clarke, 1998; Vuilleumier, 2000). Historically, the term was introduced by Babinski (1914) to refer to unawareness of hemiplegia. Anosognosia for hemiplegia is not rare after stroke (Baier and Karnath, 2005) and correlates with poor long-term outcome (Gialanella and Mattioli, 1992; Hartman-Maei *et al.*, 2001). However, the neurological, cognitive and psychological factors contributing to anosognosia for hemiplegia remain unclear. Previous studies have not identified a consistent pattern of brain lesion or dysfunction (Vuilleumier, 2004), except for a more frequent occurrence after right than left-hemisphere damage (e.g. Jehkonen *et al.*, 2006). A similar right-hemisphere predominance has been observed during Wada tests (Breier *et al.*, 1995; Carpenter *et al.*, 1995). Recent attempts to determine more precise neuroanatomical substrates have reported conflicting results, pointing to a critical role of the posterior insula (Karnath *et al.*, 2005; Baier and Karnath, 2008) or premotor cortex (Berti *et al.*, 2005), but the reasons for such discrepancies remain unclear.

Past neuropsychological studies suggest that anosognosia for hemiplegia might not be a unitary phenomenon, since many forms and degrees are encountered (for a review see Vuilleumier, 2000). It can manifest independently at the verbal and non-verbal levels, such that a patient who denies his hemiplegia may nevertheless behave adequately, for example by staying in bed. Conversely, other patients can verbally admit their handicap but act as if it did not exist (Berti *et al.*, 1996; Ghika-Schmid *et al.*, 1999). In addition, anosognosia can be selective for one deficit while another disabling impairment may be correctly recognized (Bisiach and Geminiani, 1991). Some patients may acknowledge their deficit but show a lack of concern or interest (anosodiaphoria; Babinski, 1914) as well as bizarre attitudes or beliefs concerning their paralysed limb, such as a feeling of non-belonging (asomatognosia) or delusional interpretations (e.g. somatoparaphrenia; Gerstmann, 1942; misoplegia, Critchley, 1962). Furthermore, anosognosia for hemiplegia is typically an acute phenomenon and tends to disappear within a few hours or days after stroke onset, although exceptionally, it can persist after the first 3 months (Heilman *et al.*, 1998). This time-course may explain the rarity of systematic investigations in large samples, but also account for some divergence between previous studies, and hamper direct comparisons between detailed single-case studies conducted at different times post-stroke onset. To our knowledge, no study has investigated patients from an early hyperacute stage (<3 days), when anosognosia for hemiplegia is most common, to subsequent subacute and chronic stages, when it has abated.

Anosognosia for hemiplegia: theoretical issues

Many theories and speculations have been proposed to explain anosognosia for hemiplegia over the last hundred years, but no definitive and synthetic account has yet emerged. Several influential hypothesis were put forward based on single case studies (e.g. Babinski, 1914; Heilman, 1991; Gold *et al.*, 1994; Ramachandran, 1995) or purely speculative grounds (e.g. McGlynn and Schacter, 1989; Frith *et al.*, 2000). The lack of unified theory suggests that a single general mechanism is unlikely and that anosognosia for hemiplegia may constitute a heterogeneous collection of disturbances (Marcel *et al.*, 2004) and/or a multi-componential disorder (Vuilleumier, 2004) affecting bodily awareness.

Babinski (1914) had proposed a critical role for sensory deafferentation, especially severe proprioceptive loss, however, this explanation has proved insufficient since several studies have reported dissociations between anosognosia for hemiplegia and anaesthesia (Cutting, 1978; Bisiach *et al.*, 1986; Marcel *et al.*, 2004) or proprioceptive loss (Willanger *et al.*, 1981; Small and Ellis, 1996). Likewise, anosognosia for hemiplegia is not reliably correlated with the severity of motor weakness (Starkstein *et al.*, 1992; Small and Ellis, 1996; Marcel *et al.*, 2004).

More recently, Heilman and collaborators (1991, 2000) proposed a 'feedforward' or intentional theory of anosognosia for hemiplegia. This influential hypothesis suggested that a unilateral loss of motor intention for the affected limb (Heilman *et al.*, 2000) might disrupt some 'feedforward' signals that mediate internal representations of motor actions and convey a subjective sensation of volitional effort; in the absence of such intention signals, internal comparator processes will fail to detect a mismatch between the desired and the performed motor action and hence the patient will fail to experience paralysis. In support of this idea, Gold *et al.* (1994) reported a single patient with left hemiplegia and anosognosia for hemiplegia in whom EMG recordings showed no contraction of pectoral muscles during attempts to move the left arm, although these trunk muscles receive bilateral innervations and should contract even in the presence of unilateral limb paralysis. However, EMG measures in another patient with anosognosia for hemiplegia found intact muscle activation during mental imagery of bimanual actions (Hildebrandt and Zieger, 1995). Therefore, impaired intentional motor mechanisms may not be sufficient, or such deficit may arise in some patients only.

The presence of confusion and/or cognitive dysfunction has been mentioned by several authors as a prerequisite for anosognosia, although the exact nature of such dysfunction has remained unclear or inconsistent. Weinstein and Kahn (1950) reported that their anosognosic patients were always disoriented. Levine (1990) formulated a 'discovery theory' of anosognosia for hemiplegia, according to which cognitive deficits might contribute to denial by preventing the detection of limb weakness when combined with proprioceptive or sensory loss. However, the existence of anosognosia for hemiplegia in patients with relatively preserved mental capacities was emphasized very early on (e.g. Babinski, 1914; Joltrain, 1924), indicating that the disorder might result from a more specific cognitive impairment rather than from

global mental dysfunction (McGlynn and Schacter, 1989; Bisiach and Geminiani, 1991).

An important cognitive deficit that might contribute to anosognosia for hemiplegia is spatial neglect. Several studies found a strong association between the two disorders (for reviews see Feinberg, 1997; Vuilleumier, 2000). A suppression of perceptual experience for one hemispace and/or hemibody due to spatial neglect might arguably impair the 'discovery' of the deficit. Moreover, vestibular stimulation can induce a transient recovery from both anosognosia for hemiplegia and neglect (Cappa *et al.*, 1987; Rode *et al.*, 1992). However, a number of findings suggest that anosognosia for hemiplegia is not simply another manifestation of spatial neglect. First, dissociations between the two conditions have been reported (Bisiach *et al.*, 1986; House and Hodges, 1988; Small and Ellis, 1996; Dauriac-Le Masson *et al.*, 2002; Berti *et al.*, 2005). Secondly, most patients with anosognosia for hemiplegia and left neglect still deny their weakness even when the affected limb is shown in the intact right side of space (Lu *et al.*, 2000). Finally, some patients who present with anosognosia for hemiplegia during Wada test and right-hemisphere anaesthesia do not necessarily develop neglect (Adair *et al.*, 1995). Nevertheless, personal neglect or asomatognosia (rather than extrapersonal neglect) might constitute more specific forms of unawareness for one's own body parts that could potentially contribute to anosognosia for hemiplegia (Adair *et al.*, 1995; Baier and Karnath, 2008).

An association with frontal lobe deficits (i.e. motor impersistence, mental flexibility, shifting abilities, etc) has also occasionally been observed, raising the question of their causal implication in anosognosia for hemiplegia (Starkstein *et al.*, 1992). In a recent study, Marcel and colleagues (2004) specifically tested the hypothesis of deficient mental flexibility using classical executive tests together with new procedures to assess self-monitoring abilities. Patients were asked to evaluate their own performance, based on expectations and observed outcome, for both mental and sensorimotor tasks. Results showed no significant association between anosognosia for hemiplegia and scores on classic frontal-lobe tests, but patients with anosognosia for hemiplegia typically overestimated their performance before execution, suggesting that such estimation may rely on premorbid expectations and beliefs rather than on actual state. Moreover, when self-estimation was again probed after an attempt or actual execution of the task, patients with left hemisphere lesions usually corrected their initial overestimation while patients with right-hemisphere lesions showed insufficient adjustment of their first judgement. In any case, the fact that some patients may deny a deficit while recognizing another neurological problem suggests that their lack of awareness is not associated with a general alteration of mental flexibility, but may rather involve a more specific ability to adjust knowledge and behaviour based on a direct 'first-person' experience (Marcel *et al.*, 2004; Vuilleumier, 2004).

Anosognosia has also been considered as an unconscious defence mechanism allowing patients to ignore the distress caused by their illness. Indeed, anosognosic behaviour may occur in other non-neurological conditions, such as coronary infarction and cancer (Caplan and Shechter, 1987). Even healthy people show a 'natural optimistic bias' (Diener and Diener, 1996; Beatrice and Brugger, 2002); thus Weinstein and Kahn (1955) suggested that anosognosia for hemiplegia might reflect a psychologically motivated denial, due to premorbid personality traits and emotional factors. Other evidence suggests some covert knowledge and effortful inhibition of attention towards deficit-related information (Nardone *et al.*, 2007). However, several clinical observations do not support psychological defence as a major causal mechanism in most cases. Anosognosia is, for example, almost never associated with peripheral neurological disorders that also lead to invalidating paralysis. Furthermore, anosognosia can dissociate between different limbs and deficits within the same patient. The transient disappearance of denial during vestibular stimulation (Cappa *et al.*, 1987; Rode *et al.*, 1992) is also difficult to explain with purely psychological factors. Finally, several studies failed to identify specific premorbid personality traits in patients with anosognosia for hemiplegia (Levine *et al.*, 1991; Starkstein *et al.*, 1992; Small and Ellis, 1996). Nevertheless, the role of emotional and motivational factors associated with anosognosia still remains to be more fully explored. Babinski himself noted the relationship between anosognosia for hemiplegia and lack of affective concern (anosodiaphoria). Weinstein and Kahn (1955) emphasized a reduced anxiety, lack of catastrophic reactions and affable attitudes. Other emotional changes have often been reported, including inappropriate cheerfulness and jocularity (Gainotti, 1972), apathy (Cutting, 1978, Levine *et al.*, 1991), but also depression (Starkstein *et al.*, 1990, 1992). It is possible that some brain lesions may alter emotional processes implicated in self-monitoring and adjustment to illness (Vuilleumier, 2004; Vocat and Vuilleumier, 2010), but the exact nature of these changes is unknown.

Still another cognitive model was proposed by McGlynn and Schacter (1989), who postulated a disruption between sensorimotor or perceptual modules on one hand, and the posterior 'conscious awareness system' or the 'anterior executive system' involving parietal and frontal association cortices, respectively, on the other. Accordingly, unawareness of perceptual and motor deficits (e.g. anosognosia for hemiplegia) would occur after parietal lobe damage, whereas unawareness of more complex deficits (e.g. problem solving or memory information) would result from prefrontal damage. However, this framework does not easily account for the fact that patients with anosognosia for hemiplegia are often not simply unaware, or 'disconnected' from, their hemibody impairment, but also seem strikingly 'reluctant' (or unable) to accept their failure even when directly confronted during clinical examination (Barré *et al.*, 1923; Critchley, 1953). The mechanism for this 'resistance' has still to be elucidated and might relate to additional damage to self-monitoring systems.

Finally, in keeping with the 'discovery' theory (Levine, 1990), it has been recently proposed that anosognosia for hemiplegia may not result from a single cognitive deficit, but rather constitute a heterogeneous collection of disturbances (Marcel, *et al.*, 2004) or a multi-componential disorder due to the synergetic effects of distinct deficits (Vuilleumier, 2004; Davies *et al.*, 2005) Thus, various kinds of impairments might affect a set of appreciation, belief and check abilities (ABC model; Vuilleumier, 2004) or involve a combination of abnormal experience and delusional interpretation (Davies *et al.*, 2005). Impaired 'appreciation' (A) might result from

various deficits altering the subjective experience of a given function (e.g. moving), due to sensory deafferentation, neglect, completion or phantom sensation, but anosognosia for hemiplegia would emerge only when additional deficits in putative belief (B) and check (C) systems can prevent the verification and discounting of the distorted experiential evidence and/or lead to delusional interpretations. Whether such verification and reality monitoring abilities rely on specific neural substrates associated with error detection and uncertainty monitoring (Falkenstein *et al.*, 2000; Vocat *et al.*, 2008) still remains unresolved (Vocat and Vuilleumier, 2010).

Our research

The current study concentrated on anosognosia for hemiplegia only, because it is the most common and most impressive form of anosognosia. Our aim was to evaluate the incidence, clinical presentation, timecourse and neuroanatomical correlates of anosognosia for hemiplegia in a large, unselected cohort of patients with left hemiplegia following right-hemisphere damage. For the first time, to our knowledge, we investigated patients with right-hemisphere stroke using a systematic battery of tests at different time points, using a prospective protocol from the hyperacute (<3 days) and subacute (7–10 days) stages after stroke until the more chronic stage (6 months). Specifically, we sought to determine whether anosognosia for hemiplegia was associated with any consistent pattern of clinical and anatomical features, by testing for (i) elementary neurological and neuropsychological disorders; (ii) mood and affective disturbances; (iii) timecourse of symptoms and (iv) anatomical sites of lesions.

Materials and methods

Recruitment of patients

We prospectively screened all patients who were admitted to Lausanne or Geneva University Hospitals after a first focal stroke (haemorrhagic or ischaemic), for an 18-month period (October 2005 to April 2007). Because many patients with left hemisphere damage have language problems that could disrupt their understanding or performance during testing, we recruited only patients who had a right-hemispheric stroke and a significant left arm motor impairment (see below for a description of the testing and rating scale used). Patients without objective motor deficits were not studied further. We also excluded patients with other neurological or psychiatric history, as well as those who could not be assessed appropriately (major confusion, severe clouding of consciousness or uncontrollable agitation). Overall, these criteria resulted in a group of 58 patients out of a total of 337 patients with right-hemisphere damage. Informed consent to participate was obtained from the patients or relatives according to regulations of the local ethics committee.

A primary evaluation was performed during the first 3 days after stroke (hyperacute phase), while a second assessment took place ~1 week later (7–10 days, subacute phase) and a third final testing was administered at 6 months (chronic phase).

Assessment in the hyperacute and subacute phases

A wide range of tests was administered to investigate awareness of the motor deficit, but also several neurological (e.g. motricity, proprioception, vigilance), neuropsychological (e.g. neglect, memory, mental flexibility) and psychological (e.g. mood, personality) factors that might contribute to anosognosia for hemiplegia. All tests were chosen to be given at the bedside to all patients, across a wide range of stroke severity. However, to maximize sensitivity, some of the tests differed at the different assessment phases (hyperacute, subacute, chronic; see below).

Awareness testing

To take into account the variability of anosognosia for hemiplegia, we employed two separate scales to measure awareness of motor deficits at two different moments during each evaluation: the classical '4-points' score introduced by Bisiach (1968) and a new scale, constructed from three existing instruments.

The first measure involved a score ranging from 0 to 3, reflecting the level of inquiry at which the motor deficit is acknowledged by the patient: after a general question; after a specific question about the limb; or after confrontation with a requested motor action. To rate anosognosia for hemiplegia in patients with mild impairment, questions were modified according to the severity of the deficit. For instance, if a patient with moderate weakness reported 'I have slight difficulties in moving my arm', he was scored 0 but if he stated 'I can move my arm', another question was systematically added: 'can you move your arm as usual?'. If the patient replied 'yes' to this question, a confrontation test was carried out and the Bisiach score was eventually rated 2 (for a report of a mild difficulty) or 3 (for a persistent lack of acknowledgment). But if the answer to this question was 'no, my movements are more difficult than usual', the Bisiach score was rated 1.

Our second measure was based on the Anosognosia for Hemiplegia Questionnaire of Feinberg *et al.* (2000) and included additional items from the structured interview of Nathanson *et al.* (1952) and the structured questionnaire of Cutting (1978). These items investigated other aspects of awareness such as the reasons for hospitalization, description of limb function or sensations (e.g. paralysed, weak or tired). This new scale will be referred to as the modified Feinberg scale and may provide a finer measure of the severity and nature of unawareness than the Bisiach scale (ranging from 0 to 11 points).

The Bisiach scale was always administered first to each patient, while the modified Feinberg scale was evaluated at the end of the neurological examination. To combine these two measures into a unique score for our analyses (in order to strengthen the reliability of subsequent correlation tests), we computed *z*-scores for each subject on each scale and then created a mean *z*-score value for each subject (subsequently designated as a 'composite' score of anosognosia for hemiplegia). This global score allowed us to obtain a reliable quantitative estimate of anosognosia for hemiplegia, taking into account some fluctuations in time and variability across patients, and providing a more 'continuous' scale than a dichotomous separation between anosognosics versus nosognosics. This score was thus used only for statistical purposes. Nevertheless, we note that using either the Bisiach or our modified Feinberg scale alone would not modify the general pattern of results described below. For all further statistical analyses, the measure of anosognosia for hemiplegia was always (if not specifically noted otherwise) based on this composite score.

In addition, we also used a measure of anosognosia for hemiplegia adapted from the confrontation procedure of Marcel (2004) and Berti (1996). We selected two unimanual tasks (drinking a glass of water and combing the hair) and two bimanual tasks (applauding and opening a bottle) on which the patients were asked to rate their performance from 0 to 10 before and after having to execute them (with the left and right hand separately for unimanual tasks). The patient's self-evaluations were subtracted from those of the clinician (to reflect the degree of anosognosia for hemiplegia) and averaged over the four tasks involving the left, paralysed limb, resulting in a separate score for each of the three evaluation moments (before, just after and 15 min after attempts to perform the task).

Finally, we also recorded a complementary exploratory measure of the subjective experience of symptom onset by the patients. To obtain an approximate (but systematic) assessment of this subjective experience, the patients were asked (in an open interview) during the hyperacute period to describe *a posteriori* their symptoms at the very onset of the stroke. Although potentially affected by vigilance and memory dysfunction, this exploratory measure might provide a unique proxy for the degree of awareness at this exact moment. We were particularly interested in verifying if some patients who were nosognosic 3 days after stroke nonetheless showed evidence of anosognosia at the time of symptom onset. Three aspects were systematically probed in their verbal report: (i) the perceived severity of motor deficit; (ii) the emotional reaction triggered by this event and (iii) the spontaneous attribution of causality to experienced symptoms. The reports were then rated according to these three aspects (0 for full, 1 for incomplete and 2 for absent report of the expected correct experience).

Related phenomena

We adapted the questionnaire of Cutting (1978) to probe for various disorders in bodily awareness, often associated with anosognosia for hemiplegia, including anosodiaphoria, feeling of non-belonging, strangeness, misoplegia, personification, somaesthesic and kinaesthesic hallucinations, as well as supernumerary phantom illusions. Each of these phenomena was rated as clearly present (score 2), slightly present (score 1) or absent (score 0).

Neurological testing

Motor strength of both arms was assessed by asking the patient to hold each upper limb straight in front of him for 5 s. Weakness was rated according to five levels: 0 = normal; 1 = slight fall of the arm; 2 = complete fall of the arm; 3 = inability to lift the limb but with weak residual movements and 4 = no movement of the arm at all. We considered that a patient presented a significant motor impairment of the left arm when he scored $\geq$1 on this scale.

Tactile sensation was measured using three repetitions of two types of stimulation (touch or sting) on two sites (hand or elbow), i.e. 12 stimulations in total. Discrimination errors on each stimulation was scored as 0 (correct report of site and stimulation type), 1 (wrong site or wrong stimulation type) or 2 (both site and stimulation type wrong). The scores of 12 stimulation trials were then summed.

Proprioception was assessed by applying a small movement at three joints (middle finger, wrist and elbow), three times each. Discrimination of the direction of movement was rated 0 (correct) or 1 (wrong) for a total score ranging from 0 to 9.

Vigilance was rated 0 if the patient was spontaneously awake and active, 1 if reactive but slow and 2 if unable to maintain vigilance. Orientation was tested for personal, temporal and spatial domains (from 0 to 3, one point for errors in each domain).

Perceptual extinction was assessed in two different modalities: (i) visual (by making small finger movements across the two hemifields) and (ii) tactile (by light touches on each hand, with eyes closed). For each modality, four stimulations were delivered on the right, left and both sides, in random order. The measurement of visual and/or tactile extinction was not performed if the patient presented with hemianopia and/or complete hemianaesthesia (no detection of unilateral stimulation), respectively. Motor extinction was also assessed by asking the patient to raise his shoulders (in random order; four times each on the right, left and both sides simultaneously). By testing proximal movements, this procedure provides a measure of motor initiation and intentional function during unilateral and bilateral actions even in the presence of distal weakness (Coslett and Heilman, 1989). In all extinction tests one point was scored for each omission.

Neuropsychological testing

Unilateral visuospatial neglect was assessed with several standard tests: star cancellation (subtest of the Behavioral Inattention Test; Wilson *et al.*, 1987), line bisection (Schenkenberg *et al.*, 1980) and copy of the Gainotti–Ogden figure (Ogden, 1985). Reading of a short text of four lines was also examined (number of words omitted on the left side). In addition to measures on each test, a 'composite' score of visuospatial neglect was derived from these four tasks by calculating the *z*-scores for each patient in each task and then their average. Personal neglect (impaired awareness of the contralesional side of the body) was evaluated according to the procedure of Bisiach *et al.* (1986), by asking the patient to reach his left arm with his right hand. Performance was rated on a scale of four levels: 0 for a quick reach; 1 if the right arm crossed the trunk midline but did not reach the left; 2 for a movement towards the left arm without crossing of the midline and 3 for no movement of the right arm.

To examine mental flexibility, two tasks of verbal fluency were used (categorical: names of animals; phonological: words that begin with the letter 'M'; lasting 1 min each). Scores were corrected according to age and socio-economic level following standard norms (Thuillard and Assal, 1991). We also followed the procedure of Marcel *et al.* (2004) to assess self-monitoring of non-motor performance by requesting the patients to estimate their fluency performance (i.e. number of items produced) before, just after and 15 min after the task. To quantify the patients' tendency to over/underestimate themselves, we subtracted these estimations from their real performances and computed a mean for the two fluency tasks. Mental flexibility and reasoning were also assessed with a category sorting task (Weigl, 1927), in which subjects have to classify a set of shapes according to different criteria. The higher the number of correct classifications, the better the performance (scores range from 0 to 4).

Short-term memory was examined with a classical verbal span task (Wechsler, 1981). As for the verbal fluency tasks, scores were corrected according to age and socio-economic level following standard norms (Thuillard and Assal, 1991). General long-term memory capacities were probed with a very simple test that could be easily performed in the hyperacute phase: patients had to memorize three words [from the Mini-Mental Status Examination (MMSE); Folstein *et al.*, 1975] and retrieve them after 5 min. One point was scored for each word.

Because the clinical condition of patients generally improved after the hyperacute stage, a few other tests were added to the second assessment in the subacute phase. Global cognitive functioning was measured by the MMSE (Folstein *et al.*, 1975). Finally, the Catherine Bergego scale (Azouvi *et al.*, 2003) was used to provide a standardized

assessment of neglect behaviour in everyday life. This evaluation involved ratings of several daily actions and situations by both the patient and the nursing staff. A score of anosognosia was computed as the difference between the nurse (hetero-evaluation) and the patient's ratings (auto-evaluation).

Psychological testing

To assess the role of affective factors in the ability of patients to acknowledge their deficits, we obtained several measures of mood and emotional reactivity using standard rating scales. In the hyperacute phase, we administrate a shortened version of the analogical visual scale of Norris (Norris, 1971; Guelfi *et al.*, 1989), which includes, among other mental states, measures of alertness, anxiety, optimism, concerns, mood and aggressiveness. We also included two specific questions about general worries related to the current medical situation and ongoing diagnostic investigations. A second custom-made scale was designed to be completed by carers and probed various domains of affective behaviour and reactions, including depression, anxiety, irritability, concern about illness, confabulations and hallucinations (Aybek *et al.*, 2005). The latter ratings were based on the frequency of each behaviour and ranged from 0 (absent) to 3 (always present).

Finally, in the subacute phase, we also administrated the Life Orientation Test (Scheier and Carver, 1985; Scheier *et al.*, 1994) that provides a measure of dispositional optimism, defined in terms of generalized outcome expectancies.

Follow-up testing

In the chronic phase (6 months post-stroke), we made a final assessment to investigate long-term outcome of patients with or without anosognosia. In addition to testing awareness of the motor deficit (Bisiach, Feinberg scales), we assessed awareness of visuospatial neglect using the Catherine Bergego scale (Azouvi *et al.*, 2003), as well as other remaining neurological deficits (motricity, sensation, proprioception, hemianopia, perceptual and motor extinction) and general neuropsychological functioning (orientation, neglect, memory, global cognitive abilities) using a procedure similar to those in the hyperacute and subacute phases. In addition, a few other measures were specifically obtained in the chronic phase, including the modified Rankin scale (Rankin, 1957) to evaluate handicap in daily life and the Hamilton Depression Rating Scale (Hamilton, 1967) to evaluate the presence and severity of mood changes.

Statistics

In order to determine relationships between the severity of anosognosia for hemiplegia (as measured by our composite score) and other measures derived from the neurological or neuropsychological tests, we used non-parametrical correlation analyses that were most appropriate given the asymmetrical distribution of our data (Howell, 2008). The rho of Spearman was employed, with the significant threshold fixed at $P < 0.05$. Since these non-parametric tests are conservative, no correction for multiple comparisons was applied.

These correlations were then backed up by multiple regression analyses, including different tests in a single statistical model. To do so, we compensated the inherently asymmetrical distribution of our data by using ranks in place of raw scores, and then performed classical linear regressions. In order to balance the number of variables explored against the number of samples (patients), we selected only scores from tests with the greatest theoretical relevance or showing significant correlations in preceding non-parametric tests. These selected variables included the composite score of anosognosia for hemiplegia (Bisiach and modified Feinberg; taken as the dependant variable for the regression analysis), plus somatosensory, proprioceptive and motor deficits, visuospatial neglect (composite score), perceptual and motor extinction, spatiotemporal orientation, verbal fluency (composite score from the two tasks), digit span and the word-memory task.

We also explored the evolution of each deficit over time, by inspecting changes in performance between the hyperacute and subacute phases. To allow a direct comparison between different deficits we again used *z*-scores (calculated for both periods together), which provided us with values corresponding to the severity of the deficit in different domains but now independent of the time of the evaluation and the range of their initial scale. Then, by subtracting the *z*-scores of each subject for both periods (subacute minus hyperacute), we could estimate the relative decrease of a particular deficit over time. These measures of 'decreases' on a particular test were then compared with 'decreases' on other tests (using paired Wilcoxon tests, with a significant threshold at $P < 0.05$). These comparisons enabled us to test whether any deficit showed a significantly greater/smaller decrease compared to the others. To explore whether some deficits showed a similar pattern of decrease as anosognosia for hemiplegia, we also calculated Spearman correlations between these 'decreases' and anosognosia for hemiplegia scores. Thus, we could estimate which deficits might evolve in parallel to the recovery timecourse of anosognosia for hemiplegia.

Lesion analysis

The location and extent of brain damage was delineated in each patient, based on their CT scan ($n = 35$) or MRI scan ($n = 23$), obtained after the first week post-stroke (9 days on average) and then reconstructed on a standardized brain template with the MRIcro software (Rorden and Brett, 2000). This anatomical procedure was carried out by a trained neuropsychologist and subsequently verified by a neurologist in a double-blind manner (neither of these two investigators knew the scores of the patient in the different tests). The volume of lesions was also measured with MRIcro for each patient. The obtained lesions (regions of interest) were then submitted to voxel-based lesion-symptom mapping (VLSM, Bates *et al.*, 2003; Verdon and Vuilleumier, 2010) in order to determine the critical brain regions implicated in anosognosia for hemiplegia. To this aim, we performed VLSM analysis using the composite scores of anosognosia for hemiplegia (averaged *z*-scores from the different scales), obtained for both the hyperacute and subacute phases. A similar procedure was applied to identify brain lesions associated with spatial neglect (using the composite neglect score).

An important advantage of VLSM (compared to traditional lesion overlap or group subtraction) is that it does not require patients to be classified dichotomously by lesion site or by arbitrary behavioural cut-offs. Statistical analyses of the relationship between tissue damage and behaviour (e.g. anosognosia for hemiplegia) are carried out on a voxel-by-voxel basis using a continuous rating of performance. At each voxel, patients are divided into two groups according to whether their lesion region of interest does or does not include that particular voxel. The performance of the two groups (test scores) are then compared at each voxel (with *t*-test), and the resultant statistics (*t*-values) are coded along a corresponding colour scale and mapped onto the standardized anatomical brain template (Bates *et al.*, 2003; Verdon and Vuilleumier, 2010).

Results

Recruitment and severity of motor deficit

We screened a total of 337 patients with acute stroke, among whom 58 had motor deficits and were included for subsequent testing. Exclusions were mostly due to insufficient physical symptoms (i.e. no paresis), excessive vigilance disorder or past neurological history (previous stroke or other cerebral disease). Fifty patients (22 females; mean age: 65 ± 14 years; all right-handed) were examined in the hyperacute phase [mean: 2.71 days, standard deviation (SD): 0.79, range: 1–5] and 44 patients (22 females; mean age: 63 ± 13 years; all right-handed) examined in the subacute phase (mean: 8.34 days, SD: 1.37, range: 7–12). For clinical reasons, 14 patients from the hyperacute phase could not be seen in the subacute phase (36 patients participated in both phases) and eight new patients were admitted only during the subacute phase. Only 19 patients (9 females; mean age: 59 ± 13 years; all right-handed) could be examined again in the chronic phase (mean: 223 days, SD: 61, range: 180–273). In all, 14 patients participated in all three evaluations.

Among patients who were recruited for further investigation of anosognosia for hemiplegia, the severity of motor weakness in the arm was measured at each testing session on a 5-level scale (see 'Materials and methods' section) from 0 (no motor deficit) to 4 (complete plegia); scores were found to improve significantly in the chronic stage only. The mean motor deficit score was 2.84 in the hyperacute phase (SD: 1.21, range: 1–4), 2.55 in the subacute phase (SD: 1.58, range: 0–4) and 1.16 in the chronic phase (SD: 1.50, range: 0–4). The mean motor weakness was not significantly different between the hyperacute and the subacute phases [$t(88) = 1.033$, $P = 0.328$] but became less important in the chronic phase compared to the subacute phase [$t(57) = 3.248$, $P = 0.002$] or the hyperacute phase [$t(67) = 3.575$, $P < 0.001$]. Correlations with the severity of anosognosia for hemiplegia are reported below. However, all patients from the hyperacute phase showed some motor impairment (see inclusion criteria in the 'Materials and methods' section), while three out of the 44 patients had an important motor recovery in the subacute phase, such that their strength appeared almost normal and their level of motor awareness was difficult to gauge with simple verbal questionnaires. Likewise, in the chronic phase, a similar motor improvement was observed in five out of 19 patients. Nevertheless, these patients were included in our analysis in the corresponding phase in order to avoid any overestimation of anosognosia for hemiplegia in later stages (since some patients with persisting weakness could also become nosognosic) and to ensure a longitudinal view of anosognosia for hemiplegia among patients with a right-hemispheric lesion and significant hemiplegia at onset.

Prevalence of anosognosia

In the hyperacute phase, 50% of patients with motor weakness showed no anosognosia for hemiplegia and thus scored 0 on Bisiach scale (Fig. 1). Another 18% scored 1, while 14% scored 2 and 18% scored 3. Hence, a third of patients presented with a clear lack of awareness of their motor deficits (scores 2 and 3, Baier and Karnath, 2005). In the subacute phase, 57% of patients scored 0; 25% scored 1; 11% scored 2 and 7% scored 3. By contrast, in the chronic phase, the majority (89%) now scored 0, with only 6% scoring 1, none scoring 2 and a single patient scoring 3 (5%). When considering only those patients with a significant motor deficit persisting beyond the initial examination (the majority of cases), the percentages were very similar: the subacute phase showed 52% of patients scoring 0; 28% scoring 1; 13% scoring 2; and 8% scoring 3, whereas the chronic phase showed 86% scoring 0; 7% scoring 1; 0% scoring 2 and 7% scoring 3.

Results from the modified Feinberg scale showed that in the hyperacute phase, the mean score was 2.18 (±2.75) and 44% of patients were rated >0, indicating some degree of anosognosia. In the subsequent subacute phase, the mean score was reduced to 1.53 (±2.23) but still 38% of patients were rated >0. All patients had a score of 0 in the chronic phase except for one. This modified scale was reliably correlated with Bisiach scale for both the hyperacute ($r = 0.818$, $P < 0.001$) and subacute ($r = 0.758$, $P < 0.001$) phases.

Furthermore, results from our open interview on the remembered subjective experience at stroke onset revealed that only 35% of patients were able to adequately describe the onset of their symptoms (Fig. 1). Most often, they failed to correctly lateralize the deficits (e.g. 'my two legs couldn't lift me') or they minimized them (e.g. 'I had difficulties walking' while the report of observers clearly mentioned that the patient fell to the ground). Interestingly, only 26% of cases described an emotional response at symptom onset, while many patients reported a lack of emotions ('I felt calm and everything was OK') or inappropriate emotions ('I said to myself that it would go back to normal in a few hours'). Accordingly, many patients did not think about asking for help and almost two thirds (63%) mentioned that they did not believe in a neurological cause at the onset of symptoms. Although these reports were obtained *a posteriori*, and thus potentially confounded by impairments in memory and/or vigilance, they suggest that anosognosia for hemiplegia may be extremely common at the very onset, despite the frequent abruptness of deficits.

Other measures of self-monitoring and awareness

In the confrontation test of Marcel *et al.* (2004), where patients must predict and evaluate their performance on unimanual and bimanual actions, overestimations were observed only for unimanual tasks with the left/impaired hand and for bimanual tasks. None of the patients showed overestimation in unimanual tasks with the right/unimpaired hand. Therefore, we report only data for unilateral left and bimanual actions (combined; no significant difference between the two conditions). Our results indicate that, in the hyperacute phase, only 16% of patients gave a plausible estimation (score ± 1 relative to the clinician's evaluation) prior to

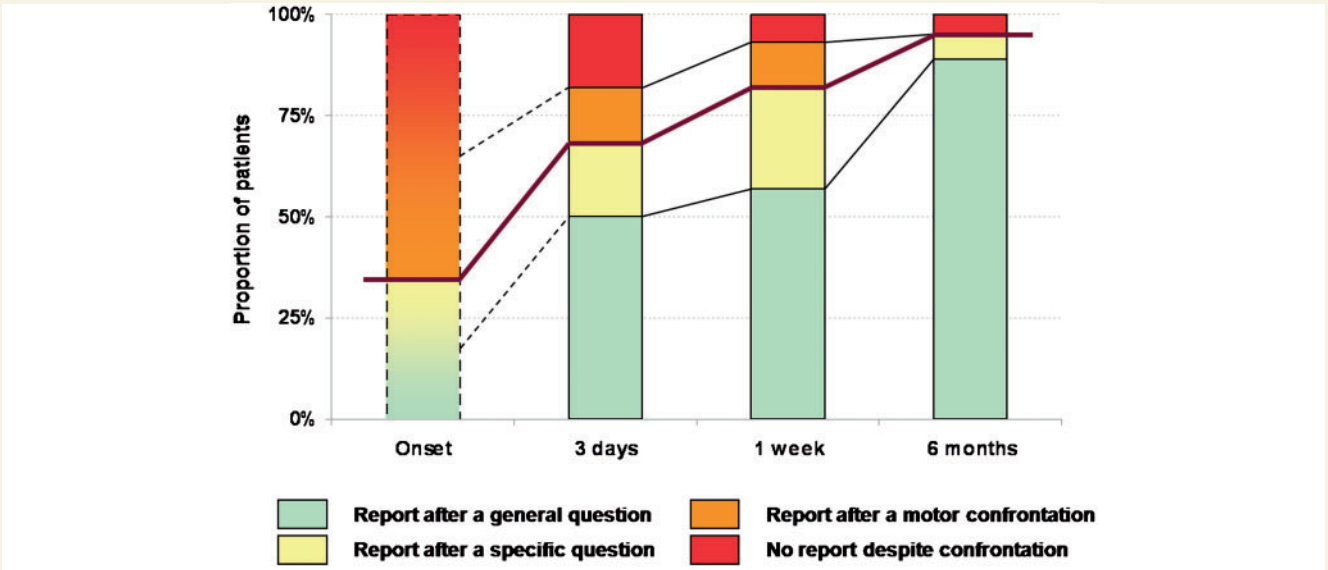

Figure 1 Evolution of awareness for the motor deficit over time (from stroke onset through to subsequent follow-up). Anosognosia for hemiplegia at stroke onset was estimated retrospectively (according to two levels: present or incomplete/absent), based on the report of remembered symptoms made by the patient during subsequent interview (in the hyperacute period). In the three other periods, anosognosia was estimated during a clinical exam and is illustrated here according to the procedure of Bisiach (four levels, see 'Materials and methods' section)—the impairment is reported after a general question (in green), after a specific question about the arm (in yellow), after motor confrontation (in orange) or not reported despite motor confrontation (in red). The purple line marks the separation between patients considered as anosognosics (Bisiach scores of 2 and 3) and those who were not (Bisiach scores of 0 and 1; Baier and Karnath, 2005). Anosognosia was present in almost two thirds of the patients at onset, but in one-third after 3 days, and in one-fifth 1 week later. After 6 months, severe anosognosia persisted only rarely.

attempting the motor task (33% just after and 34% 15 min later), while 69% of them overestimated their motor capability (54% just after and 47% 15 min later). In the subacute phase, 23% of patients provided accurate estimations (28% both just after and 15 min later), but 52% still made overestimations despite having ample time for confrontations in their daily life (53% just after and 55% 15 min later). Only one patient over-rated his motor performance in the chronic phase.

In the hyperacute phase, the mean difference between patient and clinician evaluation (patient score minus clinician score, on a scale of 0–10) was 2.74 points (±3.94) before the action, 2.19 (±3.02) just after and 2.15 (±3.40) 15 min later. In the subacute phase, these discrepancy values were 1.74 (±3.37), 1.30 (±2.35) and 1.69 (±2.63), respectively. None of these three values was significantly different from those in the hyperacute period (before: $t = 1.303$, $P = 0.196$; just after: $t = 0.793$, $P = 0.430$, 15 min later: $t = -0.193$, $P = 0.848$). Auto-evaluations of motor actions in the Marcel task were highly correlated with anosognosia for hemiplegia as measured by either Bisiach scale or our modified Feinberg score, for both the hyperacute and subacute phases ($0.597 < r < 0.763$, all $P < 0.001$).

By contrast, auto-evaluations of patients in the verbal fluency task appeared relatively normal. Indeed, the difference between the number of words given in their evaluation and those actually produced, in the hyperacute phase, was 4.07 (±12.23) before the fluency task, 1.92 (±8.83) just after and 3.38 (±13.41) 15 min later. In the subacute phase, these differences were 2.81 (±8.70), 1.60 (±7.84) and 2.12 (±8.98), respectively. These auto-evaluations of fluency performance were unrelated to anosognosia for hemiplegia scores (neither composite nor Bisiach or modified Feinberg scales alone) at any time point ($-0.170 < r < 0.169$, $0.307 < P < 0.874$). Neither were they significantly linked with motor auto-evaluations in the Marcel task ($-0.190 < r < 0.318$, $0.130 < P < 0.974$).

Finally, awareness of spatial neglect in the Bergego scale showed a marked discrepancy between patients and the nursing staff during the subacute phase ($r = 0.169$, $P = 0.430$). However, the chronic phase showed a strong relation ($r = 0.935$, $P < 0.001$) and indicated a good awareness of neglect consequences on daily activities. Interestingly, awareness of neglect was not significantly correlated with awareness of the motor deficit (anosognosia for hemiplegia composite score) in both phases ($r = 0.338$, $P = 0.098$ and $r = 0.567$, $P = 0.111$, respectively).

Related disorders of bodily awareness

Distortions in body or limb perception were common in all stages. In the hyperacute phase, 62% of patients reported some disorder of bodily awareness. The most common phenomena were anosodiaphoria (44%), kinaesthetic illusions (26%), strange feelings (14%), non-belonging (12%), misoplegia (10%), personification (8%) and supernumerary phantom (8%). Anosognosia for hemiplegia was significantly correlated with anosodiaphoria ($r = 0.445$, $P < 0.001$), but only weakly associated with kinaesthetic illusions

($r = 0.215$, $P = 0.090$) and not related to the other phenomena ($0.145 < P < 1.000$).

In the subacute phase, 58% of patients still showed related disorders. Again, they often described anosodiaphoria (36%), kinaesthetic illusions (27%), strange feelings (13%), misoplegia (13%), personification (13%), non-belonging (8%) and supernumerary phantom (8%). The presence of anosognosia for hemiplegia now showed strong correlations with kinaesthetic illusions ($r = 0.395$, $P = 0.003$) and non-belonging ($r = 0.351$, $P = 0.009$), but a weaker correlation with anosodiaphoria ($r = 0.268$, $P = 0.042$) and no relation with the other phenomena ($0.584 < P < 0.929$).

Finally, even in the chronic phase, at least one related phenomena was still present in 42% of the patients, including kinaesthetic illusions (31%), anosodiaphoria (21%), strange feelings (16%), misoplegia (10%) and non-belonging (5%). No personification or supernumerary phantoms were reported.

Correlations with other neurological and neuropsychological deficits

To explore the role of various neurological and neuropsychological deficits in the emergence of anosognosia for hemiplegia, we examined the pattern of correlations between these deficits and the severity of anosognosia for hemiplegia (as measured by our composite score combining Bisiach and other scales), using non-parametric rho Spearman tests.

In the hyperacute phase, almost all of our neurological variables were significantly correlated with the severity of anosognosia (Table 1). While correlation with motor weakness was modest ($r = 0.331$, $P = 0.019$), there were stronger correlations with tactile loss ($r = 0.603$, $P < 0.001$) and proprioceptive loss ($r = 0.620$, $P < 0.001$; with similar effects for proprioception measured at the finger, wrist or elbow), but also correlations with hemianopia ($r = 0.539$, $P < 0.001$), visual extinction ($r = 0.510$, $P = 0.003$), tactile extinction ($r = 0.504$, $P = 0.009$) and low vigilance ($r = 0.322$, $P = 0.023$). The subacute phase showed similar results for weakness ($r = 0.338$, $P = 0.033$), tactile deficit ($r = 0.397$, $P = 0.009$), proprioceptive deficit ($r = 0.358$, $P = 0.020$), hemianopia ($r = 0.313$, $P = 0.038$), visual extinction ($r = 0.564$, $P < 0.001$) and vigilance ($r = 0.373$, $P = 0.013$). Only tactile extinction ($r = 0.351$, $P = 0.100$) was no longer correlated with anosognosia for hemiplegia. Interestingly, motor extinction did not show any clear relation in both phases ($r < 0.388$, $P > 0.05$).

Among the neuropsychological variables, the severity of anosognosia for hemiplegia exhibited significant associations with spatiotemporal disorientation ($r = 0.398$, $P = 0.004$ and $r = 0.572$, $P < 0.001$) and visuospatial neglect ($r = 0.551$, $P < 0.001$ and $r = 0.600$, $P < 0.001$) for both the hyperacute and the subacute phases, respectively. Memory performance on the three-word recall task also showed a trend in the hyperacute phase ($r = 0.265$, $P = 0.082$) that became significant in the subacute phase ($r = 0.364$, $P = 0.018$), whereas personal neglect was marginally significant in the hyperacute phase ($r = 0.288$, $P = 0.045$) but not in the subacute phase ($r = -0.043$, $P = 0.782$). By contrast, all other neuropsychological tests (memory span, verbal fluency, mental flexibility) did not show any relationship with anosognosia for hemiplegia, either in the hyperacute or subacute phases ($-0.158 < r < 0.267$, $0.116 < P < 0.844$). However, the measure of global cognitive dysfunction (MMSE) in the subacute phase was significantly linked to the severity of anosognosia for hemiplegia ($r = 0.481$, $P = 0.001$).

None of the psychological and affective dimensions obtained by self-reports (e.g. mood, anxiety, personality traits; Table 1) showed a significant relationship with anosognosia for hemiplegia ($-0.285 < r < 0.181$, $0.091 < P < 0.969$). For hetero-reports by nurses in the hyperacute phase, we found that patients with anosognosia were rated as less interested in their care ($r = -0.422$, $P = 0.022$), less worried ($r = -0.402$, $P = 0.042$), more passive ($r = 0.530$, $P = 0.004$) and presenting more frequent confabulations ($r = 0.507$, $P = 0.004$). They were also considered as being more indifferent to their condition ($r = 0.356$, $P = 0.058$).

All other behaviour and mood traits (e.g. sadness, aggressiveness, crying; Table 1) showed no significant relation ($-0.347 < r < 0.202$, $0.089 < P < 0.823$). However, in the subacute phase, only the rating of 'indifference to condition' reached significance ($r = 0.422$, $P = 0.036$), while the presence of confabulations still showed a tendency ($r = 0.395$, $P = 0.069$); but none of the other ratings were significantly related to anosognosia for hemiplegia ($-0.286 < r < 0.284$, $0.169 < P < 0.870$). Finally, the questionnaire of optimism (Life Orientation Test) indicated no association with the measure of anosognosia for hemiplegia ($r = 0.127$, $P = 0.565$).

In the chronic phase, only one patient still showed a full-blown anosognosia (Bisiach score of 3). However, using a more graded measure based on the composite score of anosognosia for hemiplegia, we found significant correlations with neglect ($r = 0.532$, $P = 0.019$), spatiotemporal disorientation ($r = 0.704$, $P = 0.001$) and MMSE ($r = 0.463$, $P = 0.046$). There was no relation with the severity of tactile ($r = 0.098$, $P = 0.699$) or proprioceptive ($r = 0.216$, $P = 0.406$) impairments, nor with the measure of depression (Hamilton Depression Rating Scale; $r = 0.197$, $P = 0.420$). Interestingly however, the correlation between a measure of handicap (Rankin) and anosognosia for hemiplegia was almost significant ($r = 0.450$, $P = 0.053$).

Finally, because it is possible that a more unitary pattern of factors associated with anosognosia for hemiplegia might be found when the motor loss is more complete and severe, we repeated our analyses using only the subgroup of patients with a complete hemiplegia. This subgroup included 21 patients in the hyperacute phase and 18 patients in the subacute phase (only two patients remained completely hemiplegic in the chronic phase, preventing any statistical analyses for that period). We found globally similar results as above. For the hyperacute phase, anosognosia for hemiplegia was significantly correlated with sensation ($r = 0.485$, $P = 0.030$), proprioception ($r = 0.746$, $P < 0.001$), visual extinction ($r = 0.814$, $P = 0.004$), visuospatial neglect ($r = 0.718$, $P = 0.019$) and memory ($r = -0.452$, $P = 0.045$), but not with other neurological ($0.248 < r < 0.401$, $0.071 < P < 0.306$) or neuropsychological variables ($0.145 < r < 0.420$, $0.106 < P < 0.543$). No psychological measure reached significance ($0.029 < r < 0.467$, $0.126 < P < 0.920$). For the subacute period, these correlations failed to reach significance because too

Table 1 Correlations of anosognosia for hemiplegia with other disorders

	Hyperacute		Subacute		Chronic	
	r	*P*	*r*	*P*	*r*	*P*
Neurological						
Motricity	0.331	0.019	0.338	0.033	0.159	0.515
Sensation	0.603	0.000	0.397	0.009	0.098	0.699
Proprioception	0.620	0.000	0.358	0.020	0.216	0.406
Vigilance	0.322	0.023	0.373	0.013	–	–
Hemianopia	0.539	0.000	0.313	0.038	0.438	0.061
Visual extinction	0.510	0.003	0.564	0.000	0.412	0.089
Tactile extinction	0.504	0.009	0.351	0.100	−0.208	0.407
Motor extinction	0.319	0.148	0.388	0.055	0.347	0.205
Handicap—Rankin	–	–	–	–	0.450	0.053
Neuropsychological						
MMSE	–	–	0.481	0.001	0.463	0.046
Orientation	0.398	0.004	0.572	0.000	0.704	0.001
Memory—MMSE	−0.265	0.082	−0.364	0.018	−0.469	0.043
Personal neglect	0.288	0.045	−0.043	0.782	–	–
Visuo-spatial neglect	0.551	0.000	0.600	0.000	0.532	0.019
Span	0.072	0.634	0.267	0.116	–	–
Subtraction—MMSE	–	–	−0.158	0.317	−0.166	0.497
Flexibility	–	–	−0.038	0.844	–	–
Verbal fluency	−0.091	0.581	−0.184	0.275	–	–
Psychological						
Patient—depressed	−0.039	0.797	0.079	0.627	–	–
Patient—sleepy	−0.058	0.735	0.031	0.861	–	–
Patient—calm	−0.220	0.191	0.181	0.305	–	–
Patient—woolly	−0.046	0.785	0.122	0.494	–	–
Patient—clumsy	−0.045	0.796	−0.045	0.801	–	–
Patient—sluggish	0.075	0.662	−0.046	0.795	–	–
Patient—displeased	0.162	0.339	−0.073	0.683	–	–
Patient—anxious	0.033	0.850	−0.136	0.442	–	–
Patient—slow minded	−0.091	0.596	0.029	0.870	–	–
Patient—tensed	−0.285	0.091	−0.080	0.654	–	–
Patient—absent-minded	0.146	0.403	−0.067	0.706	–	–
Patient—incapable	−0.015	0.933	0.090	0.612	–	–
Patient—unhappy	−0.022	0.900	−0.107	0.545	–	–
Patient—hostile	−0.202	0.243	−0.057	0.749	–	–
Patient—annoyed	−0.135	0.440	0.081	0.648	–	–
Patient—withdrawn	−0.193	0.267	−0.167	0.347	–	–
Patient—concerned	0.067	0.702	−0.061	0.732	–	–
Patient—worried	−0.007	0.969	−0.049	0.784	–	–
Nurses—sad	−0.044	0.823	−0.054	0.797	–	–
Nurses—aggressive	0.202	0.292	–	–	–	–
Nurses—interested	−0.422	0.022	−0.209	0.326	–	–
Nurses—euphoric	0.120	0.536	0.035	0.870	–	–
Nurses—hallucinations	0.119	0.530	–	–	–	–
Nurses—worried	−0.402	0.042	−0.286	0.186	–	–
Nurses—crying	−0.347	0.089	0.064	0.771	–	–
Nurses—getting angry	−0.048	0.810	−0.106	0.615	–	–
Nurses—passive	0.530	0.004	0.284	0.169	–	–
Nurses—disinhibited	0.051	0.792	0.213	0.340	–	–
Nurses—confabulations	0.507	0.004	0.395	0.069	–	–
Nurses—catastrophic reaction	−0.056	0.778	−0.158	0.494	–	–
Nurses—indifferent	0.356	0.058	0.422	0.036	–	–
Optimism	–	–	0.127	0.565	–	–
Depression—HDRS	–	–	–	–	0.197	0.420

r values are non-parametric Spearman rho values for the correlation of deficits with the severity of anosognosia for hemiplegia (as measured by the composite score) for each examination phase separately. Significant correlations are highlighted in bold. HDRS = Hamilton Depression Rating Scale.

few patients ($n = 18$) could be incorporated in the analysis, but relevant trends were observed between anosognosia for hemiplegia and visual extinction ($r = 0.488$, $P = 0.075$), visuospatial neglect ($r = 0.441$, $P = 0.067$) and global cognitive functioning (MMSE; $r = -0.472$, $P = 0.056$). Sensation ($r = 0.067$, $P = 0.793$) and proprioception ($r = 0.034$, $P = 0.894$) showed no significant relationship in this period.

Multiple regression analysis

To take into account the different variables simultaneously, we ran a multiple linear regression in which we entered the main neurological and neuropsychological factors that were theoretically relevant or found to be significant in simple correlations above (see 'Materials and methods' section), together with the severity of anosognosia for hemiplegia (composite score) as the dependent variable.

For the hyperacute phase, the regression model revealed that proprioceptive loss was the only single significant deficit ($t = 3.443$, $P = 0.003$) that explained the severity of anosognosia for hemiplegia, independent of all other factors. None of the latter reached significance in this multiple regression analysis ($-1.191 < t < 1.494$, $0.153 < P < 0.791$), including the degree of visuospatial neglect ($t = 1.852$, $P = 0.809$). However, for the subacute phase, a different model emerged although the same variables were entered in the analysis. The most significant factors now included visuospatial neglect (composite score, $t = 2.605$, $P = 0.013$) and spatiotemporal disorientation ($t = 2.397$, $P = 0.021$). All other variables were not significant ($-1.199 < t < 1.360$, $0.181 < P < 0.973$), including proprioception ($t = 1.758$, $P = 0.937$). These two neuropsychological factors were also correlated with the temporal evolution of anosognosia for hemiplegia, as described below.

Temporal evolution of the deficits

To examine how deficits improved from the hyperacute to the subacute period and whether some improvements were dissociated or correlated, we compared the changes in anosognosia for hemiplegia (based on the composite score) with those in all tests that showed a significant correlation in our analyses above (in either the hyperacute or subacute phases). Pairwise Wilcoxon tests indicated no significant difference ($0.113 < P < 0.962$) between the degree of change among these tests (differences in z-scores from the two phases), indicating that all tests showed a similar amount of improvement over time (from the hyperacute to the subacute period).

Nevertheless, when looking at the pattern of parallel decreases within individual participants, using non-parametric Spearman correlation tests, we found that the recovery of proprioceptive loss ($r = 0.373$, $P = 0.042$), hemianopia ($r = 0.442$, $P = 0.013$), visuospatial neglect ($r = 0.412$, $P = 0.026$) and spatiotemporal disorientation ($r = 0.344$, $P = 0.043$) were significantly associated with the degree of improvement in anosognosia for hemiplegia. Thus, only these deficits tended to show a systematic parallel temporal evolution with respect to anosognosia for hemiplegia.

Dissociations and associations of deficits

Despite strong relationships between anosognosia for hemiplegia and other neurological or neuropsychological deficits (see above), some patients showed clear double dissociations. For example, eight patients with a maximum score of proprioceptive loss had a Bisiach score of 0. But conversely, one patient who was anosognosic (Bisiach score = 2, modified Feinberg score = 6) could still correctly report most of the proprioceptive stimuli (score = 0). Likewise, one patient with severe neglect was completely aware of his recent motor incapacity, whereas another with no sign of neglect on the four different tests claimed that he could move his left arm normally despite severe hemiplegia. These cases with anosognosia for hemiplegia but without deficit of proprioception or visuospatial neglect suggest that these deficits play a relative but not unique role in the emergence of anosognosia for hemiplegia, even though they are strongly correlated.

To test for a summation of different deficits, we also examined whether patients with anosognosia for hemiplegia but milder proprioceptive loss had more pronounced deficits in other dimensions. However, patients with anosognosia for hemiplegia (Bisiach score of 2 and 3) and showing the least important proprioceptive loss (below the median score of all anosognosics) did not have more severe impairment in neglect or other tests relative to anosognosics with higher proprioceptive loss (above the median score). The same result was obtained when comparing proprioception loss in anosognosics who had the lowest (below the median) compared to the most severe (above the median) scores in the neglect test. This was found for both hyperacute and subacute phases. However, because anosognosics usually had severe deficits on many tests, the subgroups with relatively spared function in a given domain usually contained only a few patients ($n = 2$–6), which could potentially limit these comparisons.

In fact, the number of deficits presented by a single patient, rather than just their nature, was found to be a relevant factor. Indeed, when considering that a given deficit was 'present' if the patient scored above the median of the whole group, we observed a highly significant correlation between the number of deficits and anosognosia for hemiplegia ($r = 0.635$, $P < 0.001$), for both evaluation phases (Fig. 2). Nevertheless, some combinations might produce a stronger impact on awareness of plegia than others. In particular, patients who had both severe neglect and severe proprioceptive loss (above the median) exhibited anosognosia for hemiplegia much more frequently (14/18 and 11/15) as opposed to patients who had only one of these deficits (8/16 and 6/14) or none (2/14 and 4/15; $\chi^2 > 6.74$, $P < 0.034$ for the hyperacute and subacute phases, respectively). These deficits may therefore add up (or interact) to produce anosognosia for hemiplegia.

Finally, to determine whether anosognosia for hemiplegia co-occurred with a specific pattern of deficits, we ran a factorial analysis in which z-scores from main neurological, neuropsychological and psychological tests were included together. This analysis revealed that deficits in the hyperacute phase reflected four main underlying components (Table 2). The first component included anosognosia for hemiplegia scores and overestimation in the

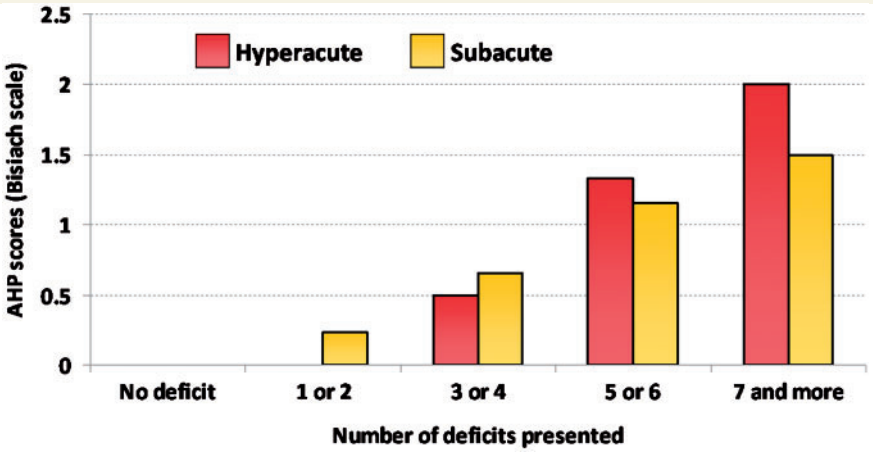

Figure 2 Mean Bisiach scores according to the number of deficits presented by patients. The deficit was considered as present if the patient scored above the median of the whole group. Ten deficits showing the strongest correlations with severity of anosognosia for hemiplegia (AHP) were taken into account here: tactile loss, proprioceptive loss, hemianopia, visual extinction, motor extinction, vigilance alteration, disorientation, memory impairment, extrapersonal neglect and personal neglect.

Table 2 Factorial analysis

Factors	Hyperacute				Subacute			
	I	II	III	IV	I	II	III	IV
Anosognosia for hemiplegia	0.793				0.719			
Marcel overestimation	0.831				0.776			
Tactile loss	0.849				0.716			
Proprioceptive loss	0.834				0.747			
Hemianopia	0.728				0.581			
Visual extinction	0.715				0.704			
Neglect	0.771				0.814			
Disorientation	0.675				0.687			
Depression		0.813				0.841		
Anxiety		0.693				0.598		
Irritability		0.868				0.742		
Memory			0.737				0.557	
Personal neglect				0.607				0.644

Deficits with a coefficient loading >0.50 on a given factor are shown for each factor and each examination phase.

Marcel task, together with most other clinical deficits including neglect, proprioceptive loss, tactile loss, visual extinction, hemianopia and orientation. A second component was specific to mood and anxiety, the third specific to memory (three-word recall) and the fourth specific to personal hemineglect. The factorial analysis for the subacute phase revealed the same four underlying components (Table 2). Again, the first component included anosognosia for hemiplegia scores and overestimation in the Marcel task together with neglect, proprioception, tactile loss, weakness, visual extinction and disorientation, whereas the second was specific to mood, the third specific to memory (three-word recall) and the fourth related to personal neglect. Thus, anosognosia for hemiplegia was generally associated with the occurrence of other neurological and neuropsychological disorders, but did not segregate into a distinct factor.

Anatomical lesion analysis

To check the validity of our approach, we first performed VLSM analyses investigating the neuroanatomical lesions that correlated with the severity of motor weakness and spatial neglect, in both hyperacute and subacute phases (Rorden and Karnath, 2004; Verdon and Vuilleumier, 2010). As expected, these analyses showed that the precentral motor cortex and the anterior part of the internal capsula were critically associated with the severity of paralysis in both the hyperacute and subacute phases (not shown). Likewise, for spatial neglect (composite score), VLSM highlighted critical regions in the posterior parietal lobe and dorsolateral prefrontal cortex for both time periods, plus the temporoparietal junction in the subacute phase (Fig. 3A and B).

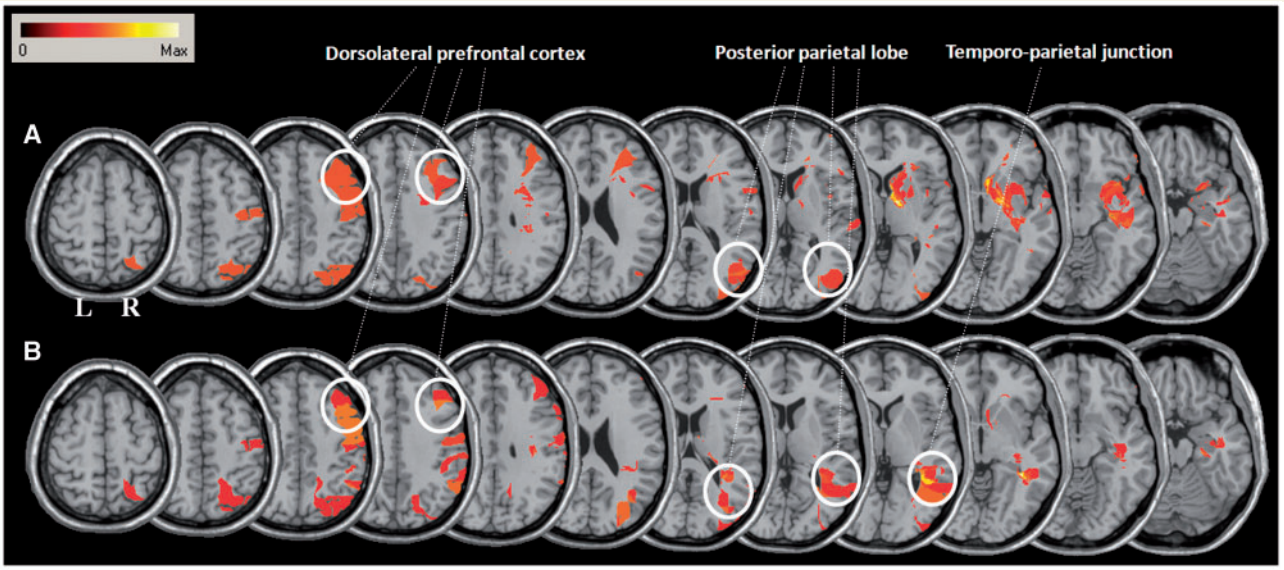

Figure 3 Voxel-based lesion mapping of left extrapersonal neglect for the hyperacute (**A**) and the subacute (**B**) phases. The voxels highlighted are those that show a significant difference ($t > 3.5$, $P < 0.001$, false discovery rate corrected) in the composite scores of extrapersonal neglect between patients with or without a lesion in these voxels. L = left; R = right.

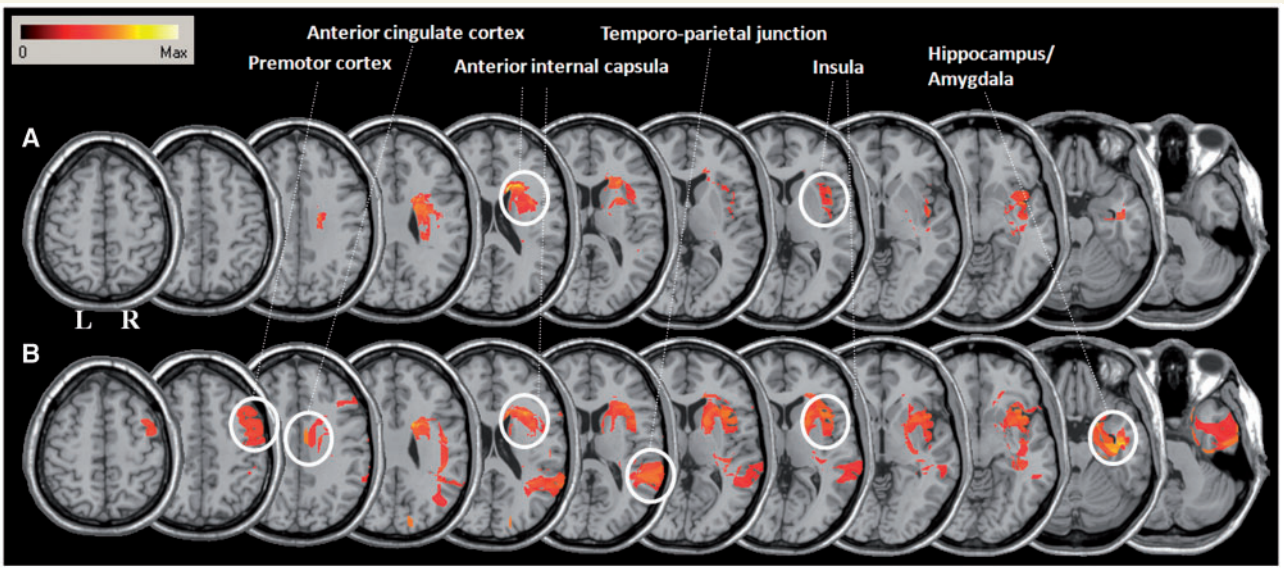

Figure 4 Voxel-based lesion mapping of anosognosia for left hemiplegia. Brain regions where damage was significantly related to the severity of anosognosia for hemiplegia in the hyperacute phase (**A**) and in the subacute phase (**B**). The voxels highlighted are those that show a significant difference ($t > 2.7$, $P < 0.01$, false discovery rate corrected) in the composite scores of anosognosia for hemiplegia between patients with or without a lesion in these voxels. L = left; R = right.

We then determined the crucial regions associated with anosognosia for hemiplegia in both periods, using the same approach (Fig. 4A and B). For the hyperacute phase, the severity of anosognosia for hemiplegia (as measured by the composite score) was correlated with damage in several brain regions, including the anterior and inferior portions of the insula (partly extending into the claustrum and putamen), together with the anterior internal capsula, rostral caudate nucleus and paraventricular white matter of the right hemisphere. For the subacute phase, additional regions were also found to be involved in the premotor cortex, dorsal cingulate, parietotemporal junction, hippocampus and amygdala.

Finally, we also tested for an effect of the size of brain damage (as determined by the number of voxels composing the lesion regions of interest in MRIcro software). The relationship with severity of anosognosia for hemiplegia was not significant in the hyperacute phase ($r = 0.297$, $P = 0.084$) but highly significant in the subacute phase ($r = 0.565$, $P = 0.001$).

Discussion

Our study is the first to follow the evolution of anosognosia for hemiplegia from stroke onset to 6 months later, using a systematic assessment of the same neurological and neuropsychological functions at different time points. Anosognosia for hemiplegia was clearly a transient phenomenon that tended to disappear with time, hence both its frequency and clinical presentation may vary depending on when patients are evaluated. Anosognosia for hemiplegia was very rare but still possible in the chronic phase (5%), while it was very common in the early hours and days after stroke. Unfortunately, some patients could not undergo testing across all three periods due to clinical constraints. Although this is unlikely to have produced systematic biases in our measures, this recruitment variability might nevertheless constitute a possible limitation for longitudinal comparisons in our study. Furthermore, due to this longitudinal view, our assessment had to take into account mild or slight motor impairment that could eventually disappear in subsequent examinations. This constraint and the fact that the diagnosis of anosognosia for hemiplegia is purely clinical might influence our measure of the frequency and severity of anosognosia for hemiplegia, despite our efforts to use the most objective and systematic approach as possible (see 'Materials and methods' section). Nevertheless, we believe that these issues were unlikely to produce major effects on the overall pattern of results and were also partly unavoidable when conducting a longitudinal study such as ours. Taken together, our results provide novel insights into the clinical course of anosognosia for hemiplegia as well as its neurocognitive and neuroanatomical underpinnings and therefore add important constraints for theoretical accounts of anosognosia for hemiplegia.

Prevalence and clinical manifestations

In the first week after stroke (subacute phase), frank anosognosia for hemiplegia (e.g. Bisiach score $\geq$2) was observed in 18% of our patients, in agreement with the rate reported by Baier and Karnath (2005), but this prevalence reached 32% within the first 3 days, and even 60% within the first few hours based on retrospective interviews. Indeed, it is striking that only one-third of our patients clearly reported a neurological cause for their symptoms when interrogated after admission, in sharp contrast with their correct description of the situational context (i.e. place, time, persons). Although the latter result is purely descriptive and might be either underestimated due to third-person reports or overestimated due to memory failure, this notion of poor insight at the very onset of stroke symptoms is consistent with other clinical reports (Grotta and Bratina, 1995) and suggests that anosognosia might be considered as a 'usual' state after severe brain damage. A more sustained and 'typical' form of anosognosia may then persist when lesions produce additional deficits in neural systems implicated in motor monitoring. In our study, anosognosia for hemiplegia was rare in the chronic period, although several chronic cases have been well documented in the literature (Cocchini *et al.*, 2002; Davies *et al.*, 2005).

Other measures of anosognosia for hemiplegia based on our modified Feinberg scale and auto-evaluations of simple motor activities (the Marcel task) also indicated a high rate of underestimation of contralesional weakness, affecting 40–50% of patients in both the hyperacute and subacute assessments. These figures might reflect minor forms of anosognosia, involving a failure to monitor and adjust to current state, rather than a true 'denial' of paralysis (Baier and Karnath, 2005). Nevertheless, these different measures of unawareness of motor deficits were highly correlated with each other at all stages (hyperacute, subacute or chronic) and revealed highly specific impairments in motor function.

Indeed, the auto-evaluation of motor performance on unimanual left and bimanual tasks was not only poor both prior and after confrontation with the task, but showed no correlation with the (relatively preserved) auto-evaluation of the same patients for their verbal fluency performance. This suggests two different monitoring mechanisms for each domain or a different role of fixed beliefs in making these judgements, because manual tasks involved familiar actions whereas fluency entailed a new cognitive exercise. Even more strikingly, we found that measures of anosognosia for hemiplegia were not significantly correlated with anosognosia for visuospatial neglect, as estimated by the Bergego scale (Bergego *et al.*, 1995), in either the subacute or chronic phases. This dissociation does not support the notion of a dysfunction or disconnection involving a single cerebral system for awareness (as proposed by McGlynn and Schacter, 1989), but rather suggests a distinct neural basis for the self-monitoring of motor abilities. Although it is possible that both anosognosia for hemiplegia and anosognosia for neglect may reflect a tendency of patients to believe that their current state accords with their past abilities (Marcel, 2004; Vuilleumier 2004), the discrepancy between unawareness of motor and spatial deficits highlights the specificity of each disorder.

Finally, we found a high prevalence of related disorders in bodily awareness (62, 58 and 42% of patients showed at least one such phenomenon in the hyperacute, subacute and chronic phases, respectively), with the most common symptoms being anosodiaphoria, kinaesthetic illusions and strangeness feelings. This high frequency is likely to reflect our systematic evaluation and suggests that these phenomena may often be otherwise missed. However, only a few of these disturbances correlated with the presence of anosognosia for hemiplegia. Such correlation concerned anosodiaphoria for plegia (in the hyperacute more than subacute phase), as well as kinaesthetic illusions and non-belonging (in the subacute more than hyperacute phase). The latter distortions in bodily awareness are intimately related to the nature of anosognosia for hemiplegia, since hallucinations of movement may promote anosognosia by depriving patients from incongruent feedback necessary to discover their deficit, and impaired awareness of deficit may in turn reduce emotional distress (anosodiaphoria). Importantly, the association with kinaesthetic illusions suggests that motor intentional processes are not necessarily suppressed in anosognosia for hemiplegia (Feinberg *et al.*, 2000). However, these associations were relatively weak, and similar disorders were often reported by patients without anosognosia for hemiplegia, indicating that they may represent worsening factors or 'collateral deficits' but be neither sufficient nor necessary to directly induce anosognosia for hemiplegia.

Overall, these data highlight the selectivity of unawareness for motor deficits, but also underscore the clinical heterogeneity of associated symptoms.

Correlations with other neurological and neuropsychological disorders

A wide range of tests was administered to patients to investigate sensorimotor and cognitive functions at different stages post-stroke. Although the choice and number of tests was necessarily limited in order to be administered at the bedside in the hyperacute and subacute phases, our prospective approach in a large group of patients allowed us to identify the pattern of neurological and neuropsychological deficits associated with anosognosia for hemiplegia, and to track their evolution in parallel to the remission of anosognosia for hemiplegia over time.

For both the hyperacute and subacute periods, we found that the degree of anosognosia for hemiplegia (on different measures) was highly correlated with the severity of several neurological disorders (particularly anaesthesia, proprioceptive loss and visual extinction) and neuropsychological disorders (particularly disorientation and visuospatial neglect). These correlations were similar when we controlled for differences in the severity of the motor impairment by taking only patients with full hemiplegia. Multiple regression analyses further indicated that proprioceptive loss and spatial neglect played the most important role (in the hyperacute and subacute phases, respectively). Impaired vigilance and motor weakness were also correlated with anosognosia for hemiplegia but only moderately. These observations are congruent with the view that multiple factors may underlie this syndrome (Vuilleumier, 2004; Orfei *et al.*, 2007), and that deficient 'appreciation' of the current state of the paralysed limb due to impaired proprioception or neglect might be a critical factor (Levine, 1990; Vuilleumier, 2004). Moreover, our factorial analysis suggested that the presence of anosognosia for hemiplegia tended to co-occur with these neurological and neuropsychological disturbances, whereas other deficits tended to occur separately—including hemianopia, memory deficit, hypovigilance and even personal neglect. The latter segregation of personal neglect into a distinct factor is particularly striking, as it indicates that it is not only different from extrapersonal neglect and proprioceptive deficits (Committeri *et al.*, 2007), but also unlikely to significantly contribute to anosognosia for hemiplegia.

In addition, we found no reliable correlation with motor extinction, again suggesting that intentional motor processes may not necessarily be impaired in anosognosia for hemiplegia, in keeping with the frequent reports of kinaesthetic illusions (see above). Likewise, anosognosia for hemiplegia was unrelated to simple tests of frontal lobe functions (flexibility and fluency) and only weakly related to memory and global cognitive functioning. The latter functions were also found to be not significant in other studies (Starkstein *et al.*, 1992; Davies *et al.*, 2005). Taken together, these results indicate that the cognitive disorders preventing the 'discovery' of paralysis in the context of an impaired appreciation of motor performance are likely to involve more specific abilities than these classic executive functions.

Importantly, we note that even though a few deficits (such as proprioceptive loss, spatial neglect, disorientation) showed a consistent co-occurrence with anosognosia for hemiplegia, this does not imply a direct causative role. Despite significant correlations, we observed a few patients demonstrating double dissociations between these deficits and anosognosia for hemiplegia. Furthermore, the number rather than just the nature of deficits in a patient appeared to predict the presence of anosognosia for hemiplegia. This pattern argues for a multi-componential model of anosognosia, but in which no single deficit is either sufficient or necessary to produce anosognosia for hemiplegia. Instead, different cocktails of deficits in different patients may lead to similar impairment in discovering and reporting plegia.

Purely psychological measures (auto- and hetero-questionnaires on personality and emotional traits) did not reveal any pattern systematically associated with anosognosia for hemiplegia. The only significant behaviours reported more often by the nurses in anosognosics were confabulations and passivity, as well as to a lesser degree a lack of interest, absence of worries and indifference. All these behaviours are closely related to the definition of anosognosia for hemiplegia itself and converge with the frequent association of anosodiaphoria (see above). However, these behaviours were mainly noted in the hyperacute but not subacute stage. This suggests that they might represent factors correlating with the 'risk' of developing anosognosia for hemiplegia, but not be necessarily present and causally linked with anosognosia for hemiplegia. Furthermore, we found no relation to states of anxiety, mood (depression or mania), angriness and even tendency to show or not show catastrophic reactions. Likewise, a measure of optimistic traits did not indicate any premorbid dispositional bias to positiveness. Hence, anosognosics made unrealistic judgements concerning their motor performance and recovery, but this 'optimism' was limited to their neurological motor ability rather than a more general attitude or personality trait. Taken together, these results do not support the suggestion that anosognosia for hemiplegia reflects a particular affective reaction to the distress induced by the deficits, although they do not rule out that emotional and motivational factors might contribute to unawareness or denial of motor weakness. More generally, our data do not support theoretical accounts of anosognosia for hemiplegia that attribute unawareness to a single cause (such as spatial or personal neglect, sensory loss, frontal dysexecutive syndrome or general optimism), even though some disturbances are more commonly associated with anosognosia for hemiplegia than others.

Evolution of anosognosia for hemiplegia

Because our prospective survey included two evaluations in the early time window post-stroke onset, when the greatest remission rate of anosognosia occurs, we were able to observe the evolution of anosognosia for hemiplegia in parallel to other impairments. As expected, all neurological and neuropsychological deficits improved after the first week. Even though the rate of improvement was generally similar across the different deficits, the pattern of decreases for anosognosia for hemiplegia was mainly correlated with the degree of change in proprioceptive loss, visuospatial neglect, disorientation and hemianopia. In other words, patients who

showed the best/worst recovery from anosognosia were those who also showed the best/worst remission in these symptoms. These results on the timecourse of anosognosia for hemiplegia thus converge with those of our multiple regression analysis and further highlight the role of proprioception disorders and neglect in anosognosia for hemiplegia during subacute stages.

Moreover, it is possible that different factors are crucial at different times. In the hyperacute phase, the more discriminative factor was proprioception, while neglect appeared more discriminative in the subacute phase. These results converge with the above to suggest that none of these neurological impairments alone is sufficient for anosognosia for hemiplegia, but the presence of multiple deficits might be needed to combine together in order to produce anosognosia for hemiplegia, with the relative importance of each factor depending on the severity of other concomitant deficits.

Finally, we found that anosognosia for hemiplegia was very uncommon in the chronic stage. Only one patient was still anosognosic at the 6-month follow-up. Nevertheless, the presence of anosognosia for hemiplegia phenomena (as measured by our composite score) was still significantly associated with neglect, but also related to more global impairments in cognitive functions (including memory and orientation).

Anatomical substrates

In agreement with clinical findings suggesting a multifactorial origin, our voxel-based lesion mapping analysis revealed that anosognosia for hemiplegia was associated with damage to a selectively distributed set of brain regions. Note that our statistical mapping approach (Bates *et al.*, 2003; Verdon and Vuilleumier, 2010) took into account the relative degree of severity of anosognosia for hemiplegia, using a continuous value (based on a composite score from two complementary scales) rather than a dichotomous classification between patients with and without anosognosia for hemiplegia and based on an arbitrary cut-off threshold (obtained from a single scale). This differs from previous attempts to identify the neuroanatomical substrates of anosognosia (e.g. Bisiach *et al.*, 1986; Berti *et al.*, 2005; Karnath *et al.*, 2005), which generally compared the overlap of lesions between two groups of patients (with versus without the disorder). Our approach might therefore be more sensitive in reflecting the clinical variety and heterogeneity of anosognosia.

For anosognosia for hemiplegia in the earliest period, we found that lesions affecting the insula (particularly its anterior part), as well as the anterior internal capsule and anterior paraventricular white matter (extending into the rostral caudate nucleus) were the most distinctive in discriminating anosognosics from nosognosics. Additional lesions in premotor areas, dorsal cingulate, parietotemporal cortex and medial temporal lobe (hippocampus and amygdala) were associated with a more persistent disorder in the later period after 1 week. Because the lesion mapping was based on neuroimaging data acquired during the first week, these results suggest that anosognosia for hemiplegia may emerge in the hyperacute phase when these additional brain areas are dysfunctional (due to ischaemic penumbra or diaschisis) but subsequently remain spared, while anosognosia for hemiplegia tends to persist in the subacute phase only when larger structural lesions are constituted, touching multiple specific regions. Consistent with this, a correlation between anosognosia for hemiplegia and total lesion size became significant only in the subacute phase.

Our findings for the hyperacute phase converge with the recent report of Karnath *et al.* (2005) that insula damage is common in patients with anosognosia for hemiplegia. In the latter study, the posterior part of the insula was found to be the most critical lesion area for anosognosia for hemiplegia, but using a different statistical mapping method. The insula is implicated in body ownership, perceived agency and interoceptive representations of body states (Craig, 2002, 2009; Critchley *et al.*, 2004). In addition, its anterior part is also involved in error monitoring (Magno *et al.*, 2006; Taylor *et al.*, 2007) and in the processing of uncertainty (Harris *et al.*, 2008). Thus, together with the anterior cingulate cortex and basal ganglia, the insula plays a key role in brain circuits necessary for monitoring performance and promoting behavioural adjustments (Ullsperger and von Cramon, 2006). These structures were also more frequently damaged in patients with anosognosia for hemiplegia, along with white matter connections in subcortical frontal regions. Damage to these circuits could therefore disrupt the neural systems normally responsible for the monitoring of motor actions and errors (Vocat and Vuilleumier, 2010). Such a disruption may prevent the cognitive and affective processing necessary for an appropriate adjustment of beliefs and checks in response to abnormal appreciation of sensorimotor state.

However, our lesion mapping results for the subacute phase revealed that other structures were also important for sustained anosognosia, including premotor areas as well as more posterior temporal and parietal areas. These findings agree with the recent study of Berti *et al.* (2005) suggesting a crucial role for the premotor cortex in anosognosia for hemiplegia (unlike Karnath *et al.*, 2005). According to these authors, premotor areas may not only mediate motor initiation and preparation but also generate a corollary signal that then serves to monitor and adjust ongoing movements by comparing a feedforward copy of motor commands with feedback information received through proprioception (Blakemore *et al.*, 2002). An impairment of this premotor area may prevent a detection of mismatch between the intended movement and the actual lack of movement in patients with anosognosia for hemiplegia. In this framework, the intention is intact as demonstrated by the preservation of proximal muscle activity on EMG (Berti *et al.*, 2007; Fotopoulou *et al.*, 2008).

In addition, damage to the right temporoparietal junction is consistent with classic neuropsychological studies that reported that anosognosia for hemiplegia and asomatognosia are common disorders after parietal lobe lesions (Bisiach *et al.*, 1986; Feinberg *et al.*, 1990). The right temporoparietal junction is critically implicated in spatial attention (e.g. Halligan *et al.*, 2003), and damage to this region leads to left hemispatial neglect (Mort *et al.*, 2003). Accordingly, neglect has often been suspected to play an important role in anosognosia for hemiplegia (Cutting, 1978; Hier *et al.*, 1983; Bisiach *et al.*, 1986; Starkstein *et al.*, 1992; Vuilleumier, 2000) and the current study clearly demonstrates that extrapersonal neglect is one of the major neuropsychological disorders correlating with both the severity and timecourse of anosognosia for hemiplegia. In contrast, we found

that personal neglect was not associated with anosognosia for hemiplegia and may have distinct anatomical correlates (Committeri *et al.*, 2007). Furthermore, a subcortical extension of lesions into the parietal white matter may be particularly harmful because it could produce both spatial neglect and proprioceptive loss due to the convergence of different fibre tracts—a combination of deficits that was commonly associated with anosognosia for hemiplegia in our study. Anosognosia for hemiplegia has also been reported after subcortical lesion due to right thalamic (Karussis *et al.*, 2000) or capsular-lenticular strokes (Bisiach *et al.*, 1986; de la Sayette *et al.*, 1995), which might induce frontal or parietal dysfunction due to disconnection or diaschisis. Notably, our VLSM analysis found that the anatomical correlates of extrapersonal neglect partly overlapped but were also clearly distinct from those of anosognosia for hemiplegia.

A less expected finding in our study was the correlation of anosognosia for hemiplegia with damage to the amygdalo-hippocampal complex in the medial temporal lobe. These regions are known to play a key role in memory and emotion. The hippocampus subserves the encoding of events in episodic memory (Squire, 1992) and lesions in this area disrupt the integration of new information into autobiographical knowledge. The amygdala is a structure critically implicated in emotional processing and learning (see Phelps and LeDoux, 2005 for a review), with a particular importance for fear (Ohman and Mineka, 2001) and, more generally, for the appraisal of self-relevant stimuli (Sander *et al.*, 2003). Thus, lesions to this structure may cause a loss of fear responses (Adolphs *et al.*, 2005) as well as an incapacity to take into account various forms of feedback that are relevant for subsequent behavioural adjustments (Ousdal *et al.*, 2008). In the case of anosognosia, it is tempting to speculate that damage to these two structures could lead to deficient processing of the abnormal or threatening feedback generated by a paralysed limb and motor failures, as well as to greater forgetfulness of these events. Consistent with this hypothesis, our results indicated a mild correlation between memory difficulties and anosognosia in the subacute (1 week) and chronic (6 months) phases. Moreover, a previous study on emotional behaviour in acute stroke showed that subjective reports of fear were reduced in anosognosic patients (Ghika-Schmid *et al.*, 1999).

To summarize, our results do not only extend but also reconcile the apparent discrepancies between previous studies on the neural bases of anosognosia, which variably pointed to the parietal lobe (Bisiach *et al.*, 1986), insula (Karnath *et al.*, 2005) or premotor areas (Berti *et al.*, 2005). We show that no single brain area seems to be sufficient by itself to produce anosognosia for hemiplegia. Indeed, no single region was damaged in 100% of patients with anosognosia. Rather, a complex network of interacting cerebral regions seems likely to be implicated in the occurrence and persistence of this disorder. The critical lesions might also act by disconnecting white matter pathways between subcortical and cortical areas in both anterior and posterior brain regions. In agreement with this, two recent meta-analyses (Pia *et al.*, 2004; Orfei *et al.*, 2007) proposed that anosognosia for hemiplegia could result from damage to neural circuits between parietal, frontal and subcortical regions that are thought to subserve motor awareness. Alternatively, the convergent evidence from clinical and anatomical results in our study indicate that lesions within this network may lead to a combination of deficits affecting proprioception, spatial attention, motor programming, action monitoring, memory and/or affective processes, consistent with the view that anosognosia for hemiplegia reflects a multi-component disorder. Each of these functions may potentially be affected in anosognosia for hemiplegia, but perhaps to different degrees or with different combinations in different patients.

However, it must be noted that anatomo-functional mapping results in our study, like those of all previous studies, were based on structural lesion data, often acquired in post-acute stages, whereas functional defects in regional cerebral blood flow have not been systematically examined during the subacute stage, when anosognosia for hemiplegia is more frequent and more severe. Future studies should exploit perfusion-based measures of brain activity to clarify the critical changes associated with anosognosia for hemiplegia and its clinical fluctuation in the early days after stoke.

Conclusion

Our prospective assessment of anosognosia for hemiplegia in a large group of patients with right-brain damage provides important insights about its multi-factorial determinants and temporal evolution. Several deficits were found to distinguish patients who were unaware or aware of their hemiplegia, involving neurological functions (i.e. proprioceptive loss, most notably in the hyperacute phase) as well as neuropsychological functions (e.g. visuospatial neglect, but also disorientation and memory impairment, most notably in the subacute phase). The latter deficits may play a key role in the production of anosognosia for hemiplegia, even though different 'cocktails' of deficits could potentially arise in different patients with anosognosia for hemiplegia. By contrast, we found that personal neglect, basic frontal lobe functions and purely psychological factors such as optimism or mood changes did not play a significant role. In accord with the notion of a multi-component syndrome, our anatomical mapping results further indicated that anosognosia for hemiplegia was associated with distributed multifocal lesions, including insula and anterior subcortical/basal ganglia regions, cingulate and premotor cortex, temporoparietal areas and amygdalo-hippocampal structures. These lesions could lead to deficits in interoceptive representations of bodily states, self-monitoring, motor programming and feedforward control and spatial attention, as well as emotional processing and learning, which might add up or interact together to disrupt motor awareness. Different degrees of damage to each of these components might also lead to different forms of anosognosia for hemiplegia and thus underlie some dissociations or variations in its clinical manifestations, such as between full denial and anosodiaphoria or between implicit and explicit recognition of the deficit (Vocat and Vuilleumier, 2010).

These results are broadly consistent with the recent 'two-factors' theory (Davies *et al.*, 2005) or ABC hypothesis (Vuilleumier, 2004) of anosognosia for hemiplegia, according to which an impairment in one or many components necessary for the 'appreciation' of the deficit (e.g. proprioception and spatial attention)

might cause anosognosia for hemiplegia (or not) depending on the severity of additional dysfunction in 'belief' or 'check' components (e.g. related to monitoring or affective processes). Thus, in some cases, anosognosia for hemiplegia might primarily arise due to a severe disruption of check components despite minor losses in proprioception and a lack of neglect. This ABC combinatorial rule would be consistent with the occasional double dissociations observed (in our study and others) between anosognosia for hemiplegia and some deficits that are otherwise strongly correlated with anosognosia for hemiplegia (e.g. spatial neglect). However, the exact cognitive processes underlying each of the ABC components and their neuroanatomical correlates still remain to be better characterized. Future studies will need to explore more specific abilities associated not only with sensory and motor functions, but also related to reasoning, belief formation, error monitoring and affective processing.

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