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Incidence, diagnosis and anatomy of

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1. Introduction

1.1 Definition of anosognosia

The term *"anosognosia"* means literally "without knowledge of disease" (a=non; nosos=disease; gnosis=knowledge) and was first described by Von Monakow (1885) whereas Babinski (1914) introduced the term "anosognosia" as a description of patients who ignored their hemiplegia.

When resting we realize that our limbs do not move and when moving we recognize that our limbs cause the action. However, this self-evident status may change dramatically following brain damage. Stroke patients with so-called *anosognosia for hemiparesis* (AHP) typically deny their paresis or behave as if the disorder did not exist. They are convinced that their limbs function normally although they have obvious motor defects. When asked to move the plegic or paretic arm or leg, they may do nothing or may move the limb of the opposite side. These patients may not even recognize their deficit even when confronted with facts that unambiguously prove the disorder (e.g. when asked to "clap the hands", no sound is heard due to the plegia of one arm). In some cases they may realize their paresis, but then consider it as harmless and state that, e.g., their leg "is tired". Other patients may experience the paretic limbs as strange or as not belonging to them ('asomatognosia'), or may even attribute ownership to another person ('somatoparaphrenia') and try to push their paralyzed limb out of the bed. Anosognosia does not only affect hemiparesis, but is also observed with cortical blindness, hemianopia, or deafness (Bisiach & Geminiani, 1991). However, when we talk about anosognosia we do not mean an illness as for example an intestinal tumor that we do not recognize ourselves as long as there is no pain or other symptoms.

Clinically, anosognosia is not a trivial problem. Failure to detect illness often delays medical care, and some of the new stroke therapies like thrombolytic therapy make early intervention important. Patients who deny hemiplegia are often reluctant to get enrolled in rehabilitation therapy, sometimes they even refuse to use a cane to walk (Ullman et al., 1960). Unawareness of deficits

might also preclude patients from recognizing their disabilities and avoiding potentially dangerous activities (Heilman et al., 1998). These aspects indicate that the diagnosis of anosognosia and the handling is an important factor to achieve better compliance and adequate medical treatment of the patient.

1.2 Anosognosia and neglect

Anosognosia and neglect are clinically difficult to separate, they are often used synonymously because the unawareness of a left hemiparesis and the failure to explore the side of space contralateral to the lesion are thought to be the same. It's described that anosognosia and neglect often occur together (Werth et al., 1986; Starkstein et al., 1992). Thus it seems that there is an association between neglect and anosognosia (Cutting, 1978; Feinberg et al., 1994; Kumral et al., 1995). Levine (1990) proposed that neglect may be a contributing factor in AHP, hypothesizing that the patient with unilateral spatial neglect is directing his attention to the ipsilesional side, so he has no opportunity to compare the vision to the right with the vision to the left. By a shift of the field of exploration to the ipsilesional field the patient may not discover the paralysis respectively the visual field defect. In the study of Starkstein et al. (1992) patients with anosognosia showed a more severe personal and hemispatial neglect. However, Bisiach et al. (1986) demonstrated a double dissociation between AHP and attentional hemispatial neglect. They point out that anosognosia for the left hemisphere "is not simply a manifestation of inattention to the left side of egocentric space and that even patients who are utterly inattentive to this side may fully appreciate their motor impairment". They made the difference between personal and extrapersonal neglect, they reported that the co-occurrence of anosognosia for motor impairment and extrapersonal neglect is more frequent than the co-occurrence of anosognosia and personal neglect. They further showed that the co-occurrence of anosognosia for hemianopia and extra-personal neglect is more frequent than the association for anosognosia and personal neglect. Overall it appears that there is a correlation between anosognosia and neglect but not a causality.

1.3 The pathogenesis of anosognosia

The pathogenesis of anosognosia is still subject of controversy. Weinstein & Kahn (1950) regarded anosognosia as a defensive psychological attitude and considered it a "manifestation of the patient's drive to be well" when he or she is facing a sudden and threatening reality such as hemiparesis after stroke. Other authors suggested that the attitude of denial is embedded in the premorbid personality (denial theory) (Guthrie & Grossman, 1952). However, there are several objections against such theories. Clinical observations that anosognosia occurs more commonly in right than in left brain damaged patients or that anosognosia does not affect all the deficits caused by stroke, but specifically just one deficit (Nathanson et al., 1952; Cutting, 1978, Starkstein et al., 1992), neither support the denial nor the psychological defense theory, and are rather in favor of a neurological theory. Furthermore anosognosia appears to be specific: a patient may have anosognosia for hemiparesis but not hemianopia. If this were a denial reaction then one would expect it to be less specific.

Early investigators like Anton (1899) and Babinski (1914) emphasize the importance of hemisensory loss, particularly loss of proprioception. According to Babinski's "feedback hypothesis" proprioceptive, undisturbed afferent sensory input is decisive for conscious perception of a body part. If sensory and in particular proprioceptive feedback was no longer able to reach areas of the brain that code the body scheme the patients were unaware that they were weak.

Another theory by Geschwind (1965) depicts anosognosia as a form of disconnection syndrome, indicating that a disconnection between the two hemispheres prevents the left hemisphere from reporting on the knowledge held about the right hemisphere. Since the left side of the body is largely controlled by the right hemisphere, only the right hemisphere would know about the paralyze of the left limb. If the left speech hemisphere is unaware of this information, then the self-report may indicate that nothing is wrong with the left arm. However there is the objection that these patients' visual input should

transfer the information to each hemisphere and should still be able to indicate non-verbal their deficit, but this does not occur in patients with anosognosia.

Heilman (1991) suggested a feedforward model of anosognosia. According to his model, weakness of the limb is recognized when there is a mismatch between the expectancy of movement and actual performance. Thus, if there is a defect in the motor system (e.g. corticospinal system or motor unit) and one tries to make a movement, the hypothetical 'monitor-comparator' notes the discrepancy between the expected movement and what is observed. However, if the patient has an intentional motor activation deficit and therefore does not intend to move, no mismatch is generated and consequently the patient does no recognize the disability. In support of this theory, was the observation that one patient with anosognosia reported making a movement even when no innervation of the muscle was seen (Gold et al., 1994). The authors concluded that no initiating attempt was made to move the hand and therefore no feed-forward respectively no feedback was detected. However another study (Hildebrandt & Ziegler, 1995) with one patient having somatoparaphrenia showed an electromyographic activity, which may reflect an initiation of the movement.

Levine (1990) suggests that a visual field defect is not phenomenally immediate but must be discovered and extends his hypothesis from the visual to the somatosensory system. He postulates that in the absence of somatosensory input, the patient does not have immediate knowledge that his limb has or has not moved. He must discover his paralysis by observing his failure in tasks requiring movement of the affected limb. While the discoveries are relatively easy for the cognitively intact person, cognitive defects and also defects in spatial attention such as neglect make discovery more difficult for the patient.

Bisiach et al. (1986) point out the modality-specificity of unawareness, and their data confirm that lack of awareness of one defect - like for example hemiplegia-may coexist with full awareness of another - like hemianopia. He states that double dissociation between unawareness of motor impairment and unilateral neglect implicates a higher level of brain activity in the way that unawareness of a defective function implies a disorder "at the highest level of organization of

that function". The implication is that "monitoring of the internal working is not secured in the nervous system by a general subordinate organ, but is decentralized and apportioned to the different functional blocks to which it refers". They suggest that the appearance of anosognosia implies damage to the neural structures outside the primary cortical areas in a modality-specific association cortex or its connections.

Quite the opposite is the model of McGlynn & Schacter (1989), postulating that immediate awareness requires activation of a supramodel system which is located in both the parietal and the frontal lobes. The parietal branch is the "conscious awareness system"(CAS) and receives input from activated function-specific cortex and mediates awareness of the activating stimulus. When the lesion disconnects the function-specific cortex from the CAS then there exists a function-specific unawareness, whereas damage to the CAS itself leads to global unawareness.

1.4 Incidence and assessment of anosognosia

In previous studies, a wide variation has been reported with respect to the incidence of anosognosia for hemiparesis ranging from 44% (Cutting, 1978) to 17% (Stone et al.,1993) in acute stroke patients. Nathanson et al. (1952) reported that 28% in a series of 100 hemiplegics showed denial of illness, including only patients with medium or severe anosognosia. Bisiach et al. (1986) reported about 33% of right brain damaged patients having anosognosia for hemiparesis. Cutting (1978) found 58% of right brain damaged patients having anosognosia for hemiparesis, while Maeshima et al. (1997) reported only about 24%. Starkstein et al. (1992) found 31% of right and left acute stroke patients with anosognosia for hemiparesis. Other studies reported incidences ranging from 17% to 28% for anosognosia for hemiparesis (Nathanson et al., 1952; Stone et al., 1993; Appelros et al., 2002). Willanger et al. (1981), considering just patients as anosognosic "if the patients without doubt denied the possibility of paresis", indicate that in their sample of 55 patients with right-sided lesions 25% did not acknowledge their hemiparesis. Anosognosia for

hemiparesis has also been assessed after intracarotid amobarbital injections (Meador et al., 2000), this study reported that 88% of 62 patients after inactivation of the non-language dominant cerebral hemisphere were unaware of their hemiparesis and 82% could not recognize their own hand at some point. Regarding the underevaluation of anosognosia in left brain damaged patients because of the presence of aphasia there is general agreement that anosognosia is more frequent following lesions of the right hemisphere. This asymmetry has been confirmed by a study of Breier et al. (1995) based on intracarotid barbiturate injection. Of the 37 patients 89% exhibited anosognosia for hemiparesis after right-side injection whereas only 49% after left-side injection.

The incidence of anosognosia for visual field deficits associated with stroke may be even higher than the incidence of anosognosia for hemiparesis (Bisiach et al., 1986) with one study (Celesia et al., 1997) estimating the incidence as 62.5% .

There are two methods of assessing impaired awareness. The first are clinical rating scales based on observing and talking to patients. The second involves comparing patients' verbal responses with the judgements of someone who has known them well before injury and who interacts with them after injury. With regard to the first method all assessment scales applied in previous studies (Critchley, 1949, Nathanson et al., 1952, Cutting, 1978, Bisiach et al., 1986) used a short interview to consider a patient "anosognosic for hemiparesis". However, so far none of the scales is generally accepted as standard procedure. One questionnaire suggested by Bisiach et al. (1986) has been widely distributed and frequently used in clinical studies (Starkstein et al. 1992, Feinberg et al. 1994, Appelros et al., 2002). In contrast to the scale of Cutting (1978), which also has been widely applied in clinical investigations (Stone et al., 1993; Jehkonen et al., 2000), the advantage of Bisiach et al.'s (1986) questionnaire is that it allows to classify the degree of anosognosia into 'mild', 'median', and 'severe' anosognosia, while the scale of Cutting (1978) only uses a dichotomous classification (having anosognosia vs. not having anosognosia). However generally accepted assessment tools are lacking.

1.5 Lesion locations

Clinicians studying computerized tomography (CT) and magnetic resonance imaging (MRI) findings of patients with anosognosia for hemiplegia have repeatedly found it difficult to localize specific lesion locations responsible for anosognosia for hemiparesis.

Several studies (Bisiach et al., 1986, Levine et al., 1991, Starkstein et al., 1992, Ellis & Small, 1997) found in patients with anosognosia for hemiparesis large lesions of the non-dominant hemisphere involving the infero-posterior parietal region, temporo-parietal cortical region and central gyri. However, subcortical lesions including thalamus, corona radiata, basal ganglia, the genu of the capsula interna, the lenticular nucleus and pons have also been reported to be critical for this phenomenon (Bisiach et al., 1986; Starkstein et al., 1992; Ellis and Small, 1997; Maeshima et al., 1997, Bakchine et al., 1997; Evyapan & Kumral, 1999). Evyapan & Kumral (1999) reported about four patients with pontine infarction in the mediolateral region showing anosognosia for hemiparesis arguing that anosognosia for hemiparesis may be due to a functional deactivation of frontal and parietal areas caused by pontine lesion (diaschisis-effect). Ellis & Small (1997) compared 30 acute stroke patients with anosognosia for hemiparesis and ten patients with hemiplegia and visuospatial neglect but without anosognosia. They plotted the lesions according to the presence or absence of infarcted tissue using the templates of Damasio & Damasio (1989) for cortical lesions, while lesions for deep structures were analyzed in Talairach space (Talairach & Tournoux, 1988). By comparing the computed tomography (CT) scans of both patient groups they found that almost all patients with anosognosia for hemiplegia had exclusively right-sided lesions, in particular in deep white matter and the basal ganglia, whereas both patient groups had lesions in the frontal areas, especially the premotor, Rolandic and paraventricular regions. They concluded that anosognosia is due to damage of neuronal circuits involving the basal ganglia, which leads to an inflexibility of the response to the lack of movement.

In conclusion, the definition of key areas generally associated with anosognosia is still a subject of controversy.

1.6 Anosognosic phenomena

Gerstmann (1942) considered anosognosia and anosognosic phenomena as indirect disorders of the body scheme since the parietal region of the major (left) hemisphere as area of central representation of the body scheme is not affected. He introduced the term _somatoparaphrenia_ and described it as "a specific psychic elaboration (marked by formation of illusions, confabulations and delusions) with respect to the affected members or side of the body, believed or experienced as absent". It is characterized by the association with a false attribution of the affected limbs to other persons after acute brain damage. _Asomatognosia_ or 'autosomatognosia', as Gerstmann (1942) called it, is referred to the inability to recognize one's own body parts, patients may experience the paretic limbs as strange or as not belonging to them. Astonishingly these absurd beliefs are often in extremely striking contrast with the intact rationality of all other thought processes. Cutting et al. (1978), considering somatoparaphrenia as "anosognosic phenomenon" found 14 patients (29%) with left hemiplegia having anosognosia phenomena without having anosognosia itself, and four patients having anosognosia and anosognosic phenomena. Using intracarotid amobarbital inactivation, Meador et al. (2000) found that anosognosia and asomatognosia showed in 88% respectively in 82% of the 62 patients during amobarbital inactivation, however, asomatognosia did also occur in the absence of anosognosia. Another study revealed that the presence of illusory limb movements, anosognosia for hemiparesis and asomatognosia are strongly associated with each other (Feinberg et al. 2000). Although anosognosia and anosognosic phenomena are regarded to be associated in some way and often occur together in particular in patients suffering severe anosognosia (Feinberg et al., 2000), it is not clear how anosognosia or anosognosic phenomena like asomatognosia and somato-paraphrenia are linked together.

1.7 The course and prognosis of anosognosia

For a majority of the patients, anosognosia for hemiparesis disappear rapidly and is often seen only in the acute phase of the stroke event (Hier et al., 1983; Maeshima et al., 1997). Maeshima et al. (1997) reported that of 12 patients with anosognosia for hemiparesis none had the symptoms in the 3 months follow-up study. Since in the anosognosia group there were periods when rehabilitation could not be performed they considered anosognosia as an inhibitory factor for rehabilitation. In another study by Jehkonen et al. (2000) none of the patients with anosognosia for hemiparesis did show anosognosia after three months neither, furthermore they reported that patients who had anosognosia acutely had a poorer functional outcome one year after illness-onset compared with the patients who were aware of their paresis.

2. Aims of the study

We wondered whether the wide variation of incidence from 17% up to 58% of right and left hemiplegic or -paretic patients might be due to varying criteria to diagnose "anosognosia for hemiparesis". According to Bisiach et al.'s (1986) scale, "mild anosognosia" for hemiparesis is diagnosed when patients do not acknowledge their paresis following a general question about actual complaints. A first aim of the present study (clinical study) was to clarify the question whether this behavior indeed should be regarded as "pathological" or still is within the normal range (especially when hemiparesis is not the only symptom that these patients suffer after stroke). Should patients who do not mention their paresis but complain about other deficits spontaneously be considered having *anosognosia for hemiparesis*?

To investigate this question the following study asked to what extent patients having "mild anosognosia" differ in their clinical parameters from patients with "medium or severe anosognosia". We further asked whether it is possible that patients with "mild anosognosia" do not acknowledge their paresis

spontaneously because other deficits exist which subjectively may have a greater impact.

The second aim was to clarify the question of key areas associated with anosognosia for hemiparesis (lesion analysis). However, the present analysis did not merely calculate the frequency of discrete regions of interest (ROIs) involved in single lesions. We rather used the entire lesioned area of each individual subject to plot the critical lesion site(s) in anosognosia for hemiparesis/-plegia and directly compared it with the control group using subtraction analysis. This allows us to illustrate the critical overlap in patients with anosognosia in direct visual contrast to those areas that do not induce anosognosia for hemiparesis.

3. Subjects and Methods

3.1 Clinical study

We investigated 128 patients with circumscribed right and left hemisphere lesions consecutively admitted from a well-defined area belonging to the University of Tübingen and 6 related community hospitals over a period of 6 months. To obtain a larger sample for the lesion analysis seven of the fourteen patients with anosognosia and two of the thirteen patients with neglect but without anosognosia were recruited from three hospitals in Munich and surroundings. Clinical examination was the same for both groups. Included were patients with acute strokes not older than 15 days who showed left- or right-sided hemiparesis or hemiplegia. Lesions were documented by magnetic resonance imaging (MRI) and/or computed tomography (CT). Patients who were not alert, not co-operative, or had severe aphasia were excluded only if communication abilities did not allow a structured interview for anosognosia (see below).

Seventy-two of the 128 patients had right brain damage, fifty-six left brain damage (Table 1). The patients gave informed consent to participate in the study, which has been performed in accordance with the ethical standards laid

down in the 1964 Declaration of Helsinki and has been approved by the ethics committee of the University of Tübingen.

All examinations were carried out right after admission, i.e. in the acute phase of the stroke.

The degree of paresis of the upper and lower limbs was scored with the usual clinical ordinal scale, with '0' for no trace of movement and '5' for normal movement. Anosognosia for hemiplegia was examined using a German translation (Karnath, 2002) of the anosognosia scale suggested by Bisiach et al. (1986): Grade 0 (no anosognosia) = The disorder is spontaneously reported or mentioned by the patient following a general question about his/her complaints; Grade 1 = The disorder is reported only following a specific question about the strength of the patient's limbs; Grade 2 = The disorder is acknowledged only after demonstrations through routine techniques of neurological examination; Grade 3 = No acknowledgement of the disorder can be obtained.

Visual field defects were assessed using standardized neurological examination. Spatial neglect was diagnosed when the patients showed the characteristic clinical behavior such as orienting towards the ipsilesional side when addressed from the front or the left and/or ignoring of contralesionally located people or objects. In addition, all patients had to demonstrate spatial neglect in the Bells test (Gauthier et al. 1989). This test consists of seven columns each containing five targets (bells) and 40 distractors. Three of the seven columns are on the left side of the DIN A4 sheet (=15 targets), one is in the middle and three are on the right (=15 targets). The patient was asked to cross out all the bells; the maximum score was 30. Omission of more than 5 bells within the three contralesional columns compared with the three on the ipsilesional side was considered indicating spatial neglect.

The patients were clinically tested for visual, auditory and tactile extinction. In each modality, 10 unilateral stimuli on either side and 10 bilateral stimuli were presented in a pseudo-random order. Visual extinction was tested by the usual clinical confrontation technique. Movements of the examiner's left and/or right index finger were presented in the patient's left and/or right visual half-field. Auditory and tactile stimulation were conducted with the patient's eyes closed.

The auditory modality was tested by rustling with a small piece of paper near the patient's left and/or right ear. Tactile extinction was investigated by applying short fingertips on the dorsal surface of the patient's left and/or right hand while the patient's arms lay relaxed in front of them. If the patient was not able to report this gentle unilateral tactile stimulation at the contralateral hand due to left-sided sensory loss, the examination was repeated with softly twitching at the left and/or right shoulder. Patients were classified as showing extinction in the respective modality when they reported $\geq 90\%$ of the unilateral stimuli on each side correctly, but failed to perceive the left stimulus during bilateral stimulation $> 50\%$ of the trials.

3.2 Lesion analysis

For the lesion analysis we selected 14 consecutive acute stroke patients admitted with right brain damage who showed anosognosia for hemiparesis/-plegia. Seven patients with anosognosia and two with neglect but without anosognosia were recruited from three hospitals in Munich. The remaining patients were from the sample of 128 patients of the University Hospital of Tübingen and 6 related community hospitals. In twelve of these patients the left arm and/or leg was plegic and many patients showed additional neurological defects such as spatial neglect, extinction etc. (Table 2). The control group thus had to be selected such that all neurological defects were present with the same frequency and severity, except for the critical variable to be investigated (i. e. anosognosia). We thus compared the anosognosia patients with a group of 13 right brain damaged acute stroke patients admitted in the same period who had no anosognosia but were comparable with respect to age, acuity and size of lesion, strength of hemiparesis/-plegia, the frequency of sensory loss, and the frequency of additional neglect, extinction, and visual field defects (Table 2). For a firm diagnosis of anosognosia for hemiparesis/-plegia only patients with grades 2 or 3 were selected. Patients in the control group had grade 0. Patients with diffuse or bilateral brain lesions as well as patients with tumors were excluded.

MR imaging was carried out in 7 stroke patients, CT scanning in 20 subjects. The initial scanning was optionally repeated during the following days until a firm diagnosis could be made and the infarcted area became clearly demarcated. These late scans were used for the present study. The mean time between lesion and the MRI used for the present analysis was 4.4 days (SD 4.3); the mean time between lesion and the CT 4.3 days (SD 2.9). To fit approximately the canonical AC-PC orientation of the MR scans, the CT imaging protocol used the line drawn between the occiput and the lower margin of the orbita to orient the scans in each individual. While being blind for the diagnosis of anosognosia, the lesions were mapped using MRIcro software (Rorden & Brett, 2000) (www.mricro.com) on slices of a T1-weighted template MRI scan from the Montreal Neurological Institute (www.bic.mni. mcgill.ca/cgi/icbm_view). This template is approximately oriented to match Talairach space (Talairach & Tournoux, 1988) and is distributed with MRIcro. Lesions were mapped onto the slices that correspond to Z-coordinates -40,-32,-24,-16,-8, 0, 8, 16, 24, 32, 40, and 50 mm in Talairach coordinates.

Since the two patient groups differed in sample size, we used proportional values for the MRIcro subtraction analysis. To identify the cortical structures that are commonly damaged in patients with anosognosia for hemiparesis but are typically spared in patients without that disorder, we subtracted the superimposed lesions of the control group from the overlap image of the anosognosia group, revealing a percentage overlay plot. Note that this subtraction technique codes the relative incidence of damage specific to anosognosia for hemiparesis. The advantage of this technique is that common lesions that are damaged with equal incidence in both groups are not highlighted.

Table 1: Demographic and clinical data of all brain damaged patients with hemiparesis or hemiplegia. Denial grade '0' to '3' according to the anosognosia scale of Bisiach et al. (1986).

		Denial grade 0		Denial grade 1		Denial grade 2		Denial grade 3	
Number		99		17		8		4	
Sex		54m; 45f		6m; 11f		6m;2f		3m;1f	
Age	Median (range)	69 (20-100)		70 (45-89)		71(51-84)		78(54-91)	
Etiology		84 Infarct		12 Infarct		3 Infarct		3 Infarct	
		15 Haemorrhage		5 Haemorrhage		5 Haemorrhage		1 Haemorrhage	
Time since lesion (d)	Median (range)	4(0-14)		4(0-11)		3.5(1-15)		3(0-14)	
Side of lesion									
Right	% present	56		41		75		100	
Left	% present	44		59		25		0	
Paresis of contralesional side	% present	100		100		100		100	
Arm	Median (range)	4(0-4)		3(0-4)		0(0-4)		0(0-1)	
Leg	Median (range)	4(0-4)		3(0-4)		0(0-3)		0(0-3)	
Visual field defects	% present	4		0		13		0	
	% t.n.p.		3		6					
Neglect	% present	16		24		75		75	
	% t.n.p.		13		12		13		25
Extinction									
Visual	% present	19		52		75		75	
	% t.n.p.		5		6		13			
Tactile	% present	22		41		75		75	
	% t.n.p.		4		12		13			
Auditory	% present	19		18		75		75	
	% t.n.p.		6		12		13			
Aphasia	% present	14		24		0		0	
MMSE	Median (range)	25(9-30)		18.5 (6-29)		13.5(10-21)		15.5(4-24)	

f, female; *m*, male; *t.n.p.*, testing not possible; MMSE, Mini-Mental Status Test (Folstein et al., 1975)

Table 2: Demographic and clinical data of all right brain damaged patients with hemiparesis/hemiplegia.

		Anosognosia	Controls	P-values
Number		14	13	
Sex		7m; 7f	8m; 5f	0.546 n.s.
Age	Median (range)	69 (47-91)	66.5 (30-80)	0.452 n.s.
Aetiology		13 Infarct	12 Infarct	
		1Haemorrhage	1 Haemorrhage	
Time since lesion (d)	Median (range)	3 (0-14)	7 (1-14)	0.293 n.s.
Time of CT/MRI since lesion (d)				
	Median (range)	3 (1-10)	2 (0-11)	0.691 n.s.
Lesion size	%RH volume	12.3 (5.9-36.4)	16.4 (0.3-28.8)	0.776 n.s.
Paresis of contralesional side	% present	100	100	
Arm	Median (range)	0(0-4)	0(0-4)	0.201 n.s.
Leg	Median (range)	0(0-4)	0(0-4)	0.807 n.s.
Sensory deficit	% present	93	77	0.268 n.s.
	% t.n.p.	7	15	
Visual field defects	% present	8	15	0.759 n.s.
	% t.n.p.	21	15	
Neglect	% present	93	92	0.956 n.s.
Extinction				
Visual	% present	78	85	0.587 n.s.
	% t.n.p.	14	15	
Tactile	% present	93	85	0.450 n.s.
	% t.n.p.	7	15	
Auditory	% present	64	69	0.785 n.s.
	% t.n.p.			

f, female; *m*, male; *t.n.p.*, testing not possible; *n.s.*, not significant.

4. Results

4.1 Clinical study

Ninety-nine (=77%) of the 128 brain damaged patients with left or right-sided hemiparesis or hemiplegia mentioned their motor deficit spontaneously following a general question about their complaints. Twenty-nine patients (23%) thus were rated showing mild, median, or severe anosognosia for hemiparesis according to the anosognosia scale of Bisiach et al. (1986). Seventeen (59%) of these twenty-nine patients had a denial grade of '1', i.e. reported their motor impairment only following a specific question about the strength of their limbs. Eight (27%) of the twenty-nine patients showed a denial grade of '2', recognizing their paresis only after demonstration, and four patients (14%) had a denial grade '3', i.e. stayed unaware of their deficit even after demonstration. Clinical and demographic variables of these patient groups are given in Table 1. One might assume that the classification of a verbal behavior scored "denial grade 1" to represent _mild anosognosia_ (Bisiach et al., 1986, Starkstein et al., 1992), could be an overinterpretation leading to an artificially high percentage of "anosognosia" in a sample of stroke patients. If such behavior instead is regarded "not pathological", one would expect that these patients do not differ with respect to clinical variables from those patients with a denial grade of '0', i.e. who had no anosognosia. Further, we expect that such patients with a "denial grade of 1" should differ from patients with denial grades '2' or '3', since both latter groups consistently do not acknowledge hemiparesis/-plegia following a specific question about the strength of their limbs (subjects with denial grade '2' only acknowledge hemiparesis/-plegia after demonstration; subjects with denial grade '3' do not recognize their hemiparesis/-plegia even after demonstration). For the following analyses, we thus polled patients with denial grades 2 and 3.

In fact, the comparison of the patient groups with denial grade '1', i.e. the 17 patients who reported their motor impairment first following a specific question about the strength of their limbs, with those showing a denial grade of '0' only

revealed a significant difference for the Mini-Mental Status Test score (MMSE) (Folstein et al., 1975) (U=410.5; p<0.001) (Table 3). All other variables such as age, severity of hemiparesis, aphasia, visual field defects, neglect, and extinction were comparable between both groups. In contrast, the comparison of patients having a denial grade of '1' with patients having a grade of '2' or '3' showed more severe paresis of the lower limb (U=48.0; p<0.001), a higher incidence of spatial neglect (χ^2=9.64; df=1; p=0.002), and more frequent auditory extinction (χ^2=10.71; df=1; p<0.001) in the latter groups. The comparison of those patients rated grade '0' with those having grade '2' or '3' revealed significant differences with respect to severity of upper and lower limb paresis, visual, tactile and auditory extinction, spatial neglect, as well as the MMSE score. Table 3 summarizes the statistical results of all comparisons.

We wondered whether those subjects who were rated having a "denial grade of 1", i.e. those patients who reported their motor impairment first following a specific question about the strength of their limbs, might not have mentioned their paretic limb spontaneously following a general question about the patients' complaints because the paresis was less severe and thus other neurological symptoms were subjectively experienced more prominently. In fact, this patient group had significantly less severe paresis with respect to those having a denial grade of '2' or '3' (Fig. 1).

To evaluate whether or not these patients mentioned other neurological defects or symptoms, which might have a greater personal impact for them, we analyzed the verbal responses of all 17 subjects. The responses were classified into four categories and each patient was assigned to one of these categories (Table 4).

Table 3: Comparison of clinical parameters between the patient groups with different denial grades. Denial grade '0' to '3' according to the anosognosia scale of Bisiach et al. (1986).

	Denial grade		
	Grade 0 versus 1	**Grade 1 versus 2/3**	**Grade 0 versus 2/3**
Age	p=0.555	p=0.710	p=0.300
Side of lesion	p=0.272	p=0.023	p=0.065
Paresis of contralesional side			p<0.001*
Arm	p=0.154	p=0.030	p<0.001*
Leg	p=0.062	p=0.012*	
Visual field defects	p=0.597	p=0.345	p=0.669
Neglect	p=0.470	p=0.002*	p<0.001*
Visual extinction	p=0.063	p=0.033	p<0.001*
Tactile extinction	p=0.548	p=0.049	p<0.001*
Auditory extinction	p=0.969	p=0.001*	p<0.001*
Aphasia	p=0.323	p=0.070	p=0.163
MMSE	p=0.001*	p=0.258	p<0.001*

* Significant with a Bonferroni corrected alpha-level: p=0.0167

In fact, following the general question about their complaints, the majority of the patients mentioned other deficits like "I had difficulties to talk" or "the hand and leg felt numb" (Table 4). One male patient with hypertrophy of his prostate mentioned that he has problems with his prostate and pain when he urinates. All of these complaints actually existed in those patients. Four patients complained about general symptoms like "tiredness", "headache" or "feeling sick" (Table 4). Two patients had no memory of the stroke event and one claimed that she came to the hospital "with the help of the ambulance after having stroke". This latter response was categorized as "inappropriate" in Table 4 since she mentioned the way in which she reached the hospital but not the reason for being hospitalized. All of the 17 patients recognized their paresis at once when the examiner asked them about the strength of their limbs.

Table 4: Categories of responses given by the 17 patients with denial grade '1' following the general question about their complaints (=first level of severity of anosognosia in the anosognosia scale of Bisiach et al. (1986)). The response of each of the 17 patients was assigned to only one of the four categories.

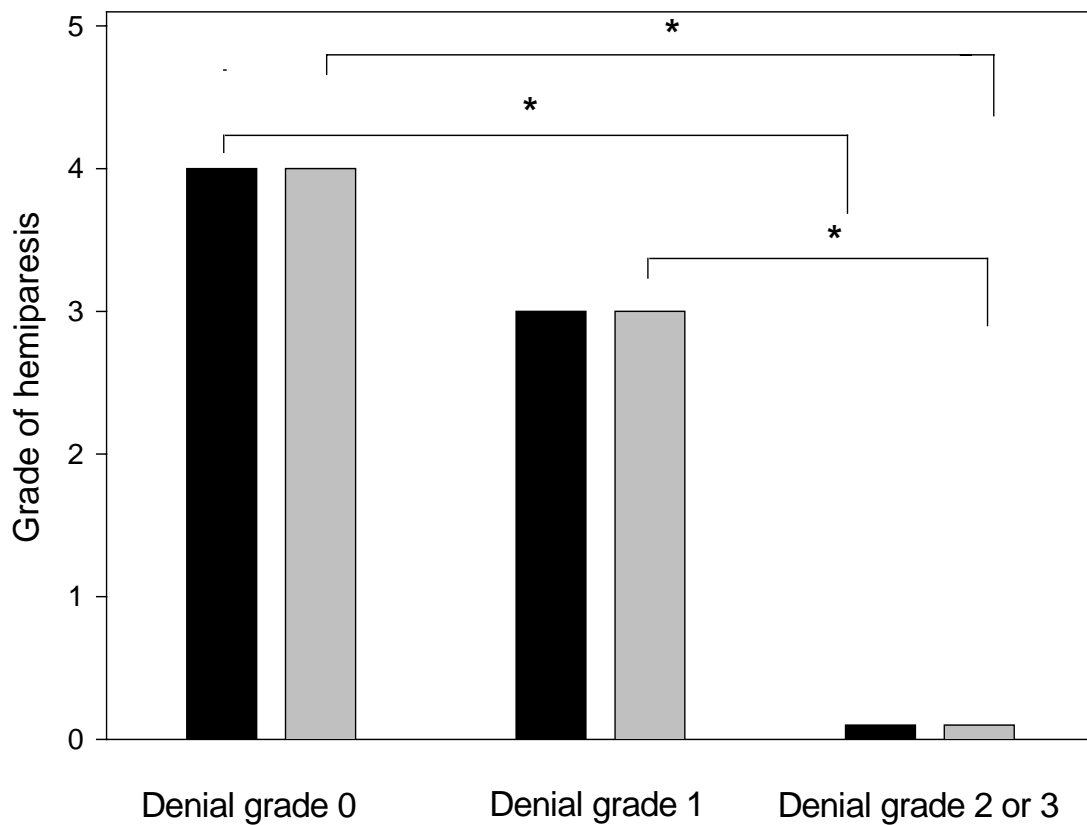| Category	
Other deficits Patients reported about speech arrest, dysarthries, sensory deficit, ptosis, facial paresis, etc.	59% (n=10)
General symptoms Patients reported tiredness, dizziness, headache, etc.	23% (n=4)
No memory Patients reported to have no memory for the stroke event.	12% (n=2)
Inappropriate response	6% (n=1)

Figure 1

Median severity of contralesional hemiparesis. Black bars indicate scores for the upper limb; grey bars for the lower limb. The degree of paresis was scored with the usual clinical ordinal scale, where '0' stands for no trace of movement and '5' for normal movement. Anosognosia for hemiplegia was examined using a German translation (Karnath, 2002) of the anosognosia scale suggested by Bisiach et al.(1986). Asterisks indicate significant differences using a Bonferroni corrected alpha-level of p=0.0167.

4.2 Lesion analysis

Figure (2a) illustrates a conventional lesion density plot for each group of patients. The number of overlapping lesions are colour coded with increasing frequencies from violet (n=1) to red (n=maximum number in the respective group). In both groups, we found lesions including temporal and parietal cortex, the insula and subcortically the basal ganglia and deep white matter.

To identify the cortical structures that are commonly damaged in patients with anosognosia for hemiparesis but are typically spared in patients without anosognosia, we subtracted the superimposed lesions of the control group from the overlap image of the group with anosognosia, revealing a percentage overlay plot (Fig. 2b). Using the anatomical parcellation of the MNI single-subject brain by Tzourio-Mazoyer et al. (2002) implanted in MRIcro (www.mricro.com), we found such an area in the right posterior insula (Fig. 2b). In fact, this area had been damaged in all (=100%) of the consecutively admitted patients with anosognosia for hemiparesis.

Figure 2

(A) Overlay lesion plots of the patients with anosognosia for hemiparesis (n=14) and of the patients with right brain damage without anosognosia (n=13). The number of overlapping lesions is illustrated by different colors coding increasing frequencies from violet (n=1) to red (n=maximum number of subjects in the respective group). Talairach z-coordinates (Talairach & Tournoux, 1988) of each transverse section are given.
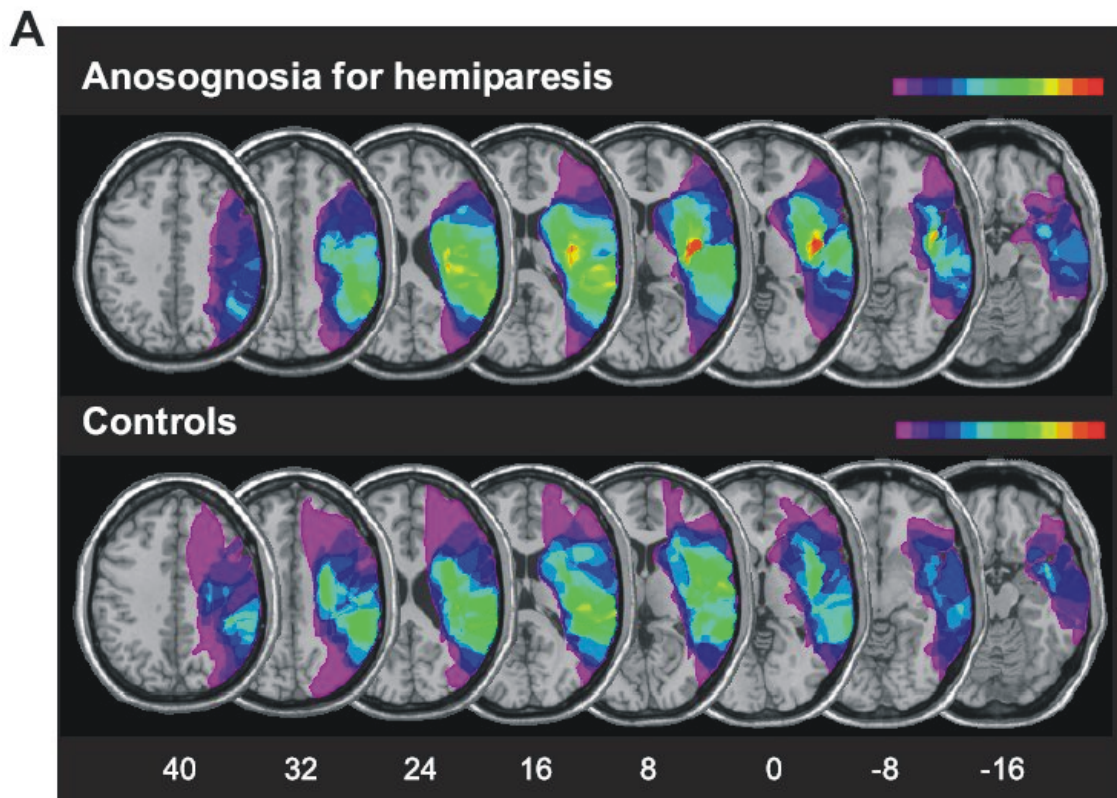
Figure 2

(B) Overlay plot of the subtracted superimposed lesions of the patients with anosognosia for hemiparesis minus the control group. The percentage of overlapping lesions of the anosognosia patients after subtraction of controls is illustrated by 5 colors coding increasing frequencies from dark red (difference = 1% to 20 %) to white-yellow (difference = 81% to 100%). Each color represents 20% increments. The center of overlap represents regions that are damaged _at least_ 40% more frequently in patients with anosognosia for hemiparesis than in controls (outlined with a white contour). The colors from dark blue (difference = -1% to -20%) to light blue (difference = -81% to -100%) indicate regions damaged more frequently in control patients than in patients with anosognosia. Wh. mat., white matter.

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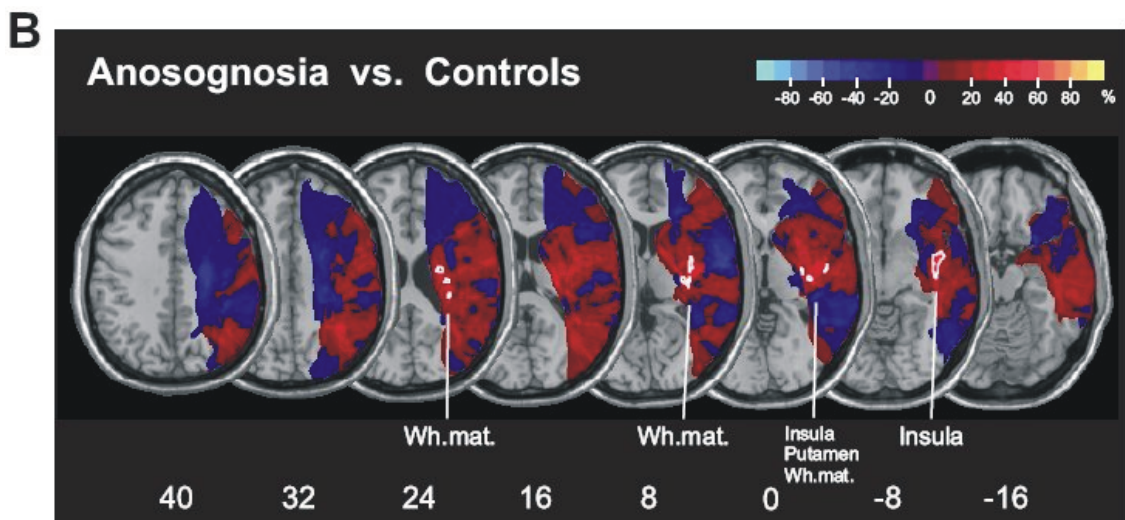
5. Discussion

First, the present study investigated if patients who do not mention their neurological defect (hemiparesis) spontaneously, but directly when addressed by the examiner, should be regarded as 'anosognosic'. In particular, we asked whether hemiparetic stroke patients diagnosed as having denial grade '1' according to the anosognosia scale of Bisiach et al. (1986) should be considered having "mild anosognosia" for hemiparesis or should rather be regarded as "not pathological". Second, a lesion analysis of stroke patients with anosognosia for hemiparesis/-plegia was made and compared with patients not having anosognosia.

Previous studies showed that patients with anosognosia differ significantly from patients without anosognosia in clinical variables with respect to side of lesion, additional neglect, and extinction (Cutting, 1978; Starkstein et al., 1992; Nathanson et al., 1952). In contrast to these findings, the present study found a high similarity between patients with denial grade '0' (= no anosognosia for hemiparesis) and those having denial grade '1'. Except for the MMSE score, we found no significant differences between these two groups for any of the clinical variables tested.

The question arises why patients rated grade '1' did not mention their paresis spontaneously. Is it possible that they simply did not mention their paretic limb because the paresis was mild and/or other deficits were subjectively more prominent? In fact the paresis of patients with denial grade '1' was significantly milder than the paresis of patients with denial grade '2' or '3'. Moreover, analysis of the verbal responses revealed that 59% of the patients with denial grade '1' complained spontaneously about other neurological deficits such as speech arrest, dysarthries, sensory deficit, ptosis etc. All these symptoms did in fact exist in these patients. Additional 35% of the grade '1' group mentioned spontaneously symptoms such as tiredness, dizziness, headache, loss of memory of the stroke event etc. Such symptoms indeed are common in stroke patients (Rathore et al., 2002; Handschu et al., 2003) and thus may be assumed to be real and not just pretended. In conclusion, the data

suggest that 94% of those patients rated "denial grade 1" did not appear to have a problem in realizing their hemiparesis but simply perceived other symptoms as being more prominent when asked a general question about their complaints. When the strength of their limb was addressed by the examiner, all these patients immediately acknowledged their paresis. In contrast, when those patients with denial grade '2' and '3' were asked specifically about the strength of their limb, they insisted that everything was alright. In conclusion, we think that a denial grade of at least '2' seems to be the appropriate cut-off for the diagnosis of "anosognosia for hemiparesis".

Provided that we consider patients with denial grade '1' as "not pathological" and only regard patients with denial grade '2' or '3' as having anosognosia, the present study would reveal an incidence of 10% anosognosia for hemiparesis in a sample of 128 acute stroke patients. Applying the same cut-off post - hoc to previous studies on this issue leads to a more homogeneous incidence for anosognosia in patients with hemiparesis. Starkstein et al. (1992) investigated a sample of 80 patients for anosognosia for hemiparesis. If these authors had considered only those patients with denial grade '2' or '3' as anosognosic, they would have revealed an incidence of 18% anosognosia for hemiparesis. Appelros et al. (2002), who used the same anosognosia scale as Starkstein et al. (1992), would have obtained an incidence of 12% of patients with anosognosia for hemiparesis.

In conclusion, we suggest that patients who do not mention their paresis spontaneously following a general question about their complaints but directly when addressed by the examiner, should not be considered having 'anosognosia'. The present study revealed that the majority of such patients suffer from and report other deficits which obviously are more prominent for the subject. These patients have a significantly milder paresis compared to those patients denying their disorder even when specifically asked about the limbs. Moreover, the clinical parameters of such patients do not differ from patients who report their disorder spontaneously.

If the present cut-off criterion is applied to our as well as post - hoc to previous data sets of other groups, we reveal very similar values for the incidence of

anosognosia for hemiparesis ranging from 10% to 18% in unselected samples of acute stroke patients with hemiparesis or hemiplegia. The incidence of anosognosia for hemiparesis thus seems to be less frequent than previously assumed (Bisiach et al. 1986, Starkstein et al. 1992, Stone et al., 1992, Appelros et al., 2002).

The second finding of the present study revealed that the posterior insula is commonly damaged in all patients with anosognosia for hemiparesis but is spared in hemiparetic patients without anosognosia who were comparable with respect to age, acuity and size of lesion, strength of hemiparesis/-plegia, and the frequency of additional neglect, extinction, and visual field defects.

The human insula is an island of cortical tissue beneath the frontal and temporal lobes which consists of four to six gyri encircled by the insular sulcus and is divided by the central insular sulcus into an anterior and posterior part. The anterior part of the insula consists of an agranular-allocortical area which is considered to be part of the paralimbic cortex (Mesulam & Mufson, 1985). The posterior part of the insula has a granular-isocortical area which is linked to the somatomotor system (Flynn et al., 1999). In between the anterior and posterior insula lies the dysgranular insula, representing an anatomical and functional transition zone. The cortical connections of the anterior part are mainly with other allocortical areas. While the anterior part has more extensive connections with limbic, paralimbic, olfactory, gustatory and autonomic structures, the major efferent projections of the posterior insula include those with the primary and second somatosensory area (SI, SII), the superior and inferior temporal cortex, the amygdala, the thalamus, the cingulate gyrus, the basal ganglia in particular the ventral claustrum, the auditory cortex (AI, AII) and the presupplementary and supplementary motor areas (Augustine, 1996, Flynn et al., 1999). The posterior insula receives afferent projections from SI as well as SII and the premotor and supplementary motor area (Flynn et al., 1999). These projections may be arranged in a way which could be related to a body map (Mesulam et Mufson, 1985) and due to the large somatosensory input of the dorsocaudal part of the insula it has been suggested that the posterior insula might represent a somatosensory as well as a motor association area (Mesulam & Mufson,

1985; Augustine, 1996). Neurons in this area showed responsiveness to auditory and to somatosensory stimulation, the latter with large fields covering the limbs, trunk, or entire body (Schneider et al., 1993). Stimulation of the posterior insula elicited gross movements (Showers and Laucer, 1961) as well as restricted movements of single muscles or small groups of muscles (Sugar et al., 1948). Furthermore, lesion studies in humans suggested that the posterior insula might represent the human vestibular cortex (Brandt et al., 1984, 1985), might be involved in language and articulation processes in the left hemisphere (Dronkers, 1996; Cereda et al., 2002), may play a role in post-stroke recovery of motor function (Chollet et al., 1991, Weiller et al., 1992) and in processes of spatial exploration and orientation in the right hemisphere (Karnath et al., 2004). Interestingly in accordance with the present findings, activity of the insula has been observed when subjects recognize aspects of themselves, suggesting a significant role of the insula in integrating different input signals related to self-awareness.

Fink et al. (1996) reported activation of the insula when subjects identified their own memory. Further, activation in the anterior insula was found when subjects attributed an action to themselves (Farrer & Frith, 2002). Specifically, involvement of the right posterior insula was observed when subjects had to indicate whether movements they saw corresponded to their own executed movements or were controlled by someone else (Farrer et al., 2003). The authors found a reduced activity of the right posterior insula going along with a decreasing feeling of controlling the movement. The activity in the right posterior insula was low when subjects experienced a mismatch between what they did and what they saw, whereas the activity was high when the afferent input matched the action. Based on these imaging results in healthy subjects, lesion of the posterior insula would be expected to cause disturbance of the feeling of being vs. not being involved in a movement and may even disturb the subject's believes about ownership and function of body parts. However, since a role of the insula for anosognosia has not been known so far, the question comes up how plausible it is to assume that such a small, circumscribed area as the posterior insula is the decisive structure to cause anosognosia for hemiparesis?

In fact, it is striking that _all_ of our 14 consecutively admitted stroke patients who were convinced that their contralesional limbs function normally despite hemiplegia or –paresis, had a lesion of exactly this brain region. However, each individual lesion also affected structures including temporal and parietal cortex, basal ganglia and deep white matter beyond the posterior insula. Temporal and/or parietal cortex, basal ganglia and/or deep white matter were likewise involved. Facing the present conclusion that the posterior insula is the relevant neural structure for anosognosia for hemiparesis the question arises whether – if not in the present patient sample – evidence has been observed that a small lesion restricted to the posterior insular cortex might suffice to cause anosognosia. Although a lesion confined to the insular cortex is a rare finding in neurological patients, a recent study in fact has reported anosognosic phenomena associated with such lesion.

To characterize the clinical consequences of acute strokes restricted to the insula, Cereda et al. (2002) identified among 4800 consecutive patients from the Lausanne Stroke Registry admitted between 1990 and 1999 all subjects who had a CT or MRI documented lesion restricted to the insula. The authors found four subjects with such locations. Two had right-sided, two left-sided insular strokes. Among the two patients with right hemisphere damage in fact one showed asomatognosia and somatoparaphrenia. This 75-yr-old right-handed woman was hospitalized after she woke up suddenly in the night with a sensation of being touched by a stranger's hand and alarmed by a foreign body in her bed (somatoparaphrenia), not recognizing her own left upper limb. Diffusion-weighted MRI showed a right posterior insular stroke. Neurological examination revealed hypesthesia for touch and pain of the left upper extremity, alteration of graphesthesia, and stereognosis. She further presented dizziness and her gait was insecure. Although anosognosia and anosognosic phenomena like asomatognosia or somatoparaphrenia are regarded to be associated in some way and often occur together in particular in patients suffering severe anosognosia (Feinberg et al., 2000), it is not clear how anosognosia or anosognosic phenomena are linked together. It may be possible that the decisive factors necessary for developing anosognosia are sensory combined

with motor deficits e.g. lesion of the posterior insula causing sensory deficit and lesion of other structures like capsula interna or parietal cortex leading to hemiparesis. Thus patients as described by Cereda et al. (2002) having exclusively lesion in the posterior insula only have sensory deficits and may therefore show only anosognosic phenomena like asomatognosia or somatoparaphrenia.

Further observations support the hypothesis that the posterior insula may be a decisive structure in the pathogenesis of anosognosia, asomatognosia, and somatoparaphrenia. It has repeatedly been reported that caloric vestibular stimulation in patients with right brain damage using cold water in the contralesional left external ear canal induced transitory remission of anosognosia for hemiparesis and of anosognosic phenomena like somatoparaphrenia (Cappa et al., 1987; Vallar et al., 1990, 2003; Bisiach et al., 1991; Rode et al., 1992, 1998). Cappa et al. (1987), treating four patients with hemineglect and anosognosia for hemiplegia with caloric stimulation, found an improvement of anosognosia in two patients. On the initial CT one patient showed a thalamocapsular haematoma, the other a hypodensity in the right insular region. Similar to our patients, both had sensory deficits on the contralesional side. Bisiach et al. (1991) and Rode et al. (1992) reported about patients with right-hemisphere stroke having neglect, anosognosia for hemiparesis and somatoparaphrenia that under the effect of vestibular stimulation these patients demonstrated a transitory remission of their somatoparaphrenia. Interestingly, positron emission tomography (PET) revealed, that this type of vestibular stimulation on the left side induces activation predominantly of the right posterior insula, as well as the right temporoparietal junction, SI and SII, retroinsular cortex, putamen, and anterior cingulate cortex (Bottini et al., 1994, 2001; Emri et al., 2003). Bottini et al. (2001) also implicate an association between the SII and the processing of vestibular stimulation. This association was also shown by Vallar et al. (1990), who demonstrated that vestibular stimulation induced a temporary remission of hemianesthesia in three right brain damaged stroke patients. In one of these patients vestibular stimulation induced a temporary complete remission of

anosognosia. Thus the posterior insula may be the binding link between the vestibular system and anosognosia for hemiparesis, offering an explanation of the effect of remission of vestibular stimulation on anosognosia and anosognosia related phenomena. Suzuki et al. (2001), using functional magnetic resonance imaging (fMRI), found also an activation of the contralateral insular cortex during caloric stimulation. They observed activation of the right insular cortex with left-ear irrigation and vice versa. Moreover, they identified the intraparietal sulcus, superior temporal gyrus, hippocampus, cingulate gyrus, and thalamus as regions activated in response to caloric vestibular stimulation. Using galvanic vestibular stimulation at the mastoid, Fink et al. (2003) observed activation of the posterior insula extending into the superior temporal gyrus and inferior parietal cortex bilaterally.

Thus, it seems as if damage of the right posterior insula induces anosognosia for hemiparesis and anosognosia related phenomena, while activation of this and surrounding regions induces remission of these symptoms. The posterior insula might represent a somatosensory as well as a motor association area as well as a limbic integration area (Mesulam & Mufson, 1985; Augustine, 1996). With respect to the former view the present data might indicate that the decisive factor causing anosognosia is a sensory integration defect, leading to pathological beliefs about function and ownership of contralateral limbs. This interpretation would be close to Babinski's (1918) "feedback-hypothesis", suggesting that undisturbed afferent sensory input is decisive for conscious perception of a body part and loss of sensibility the crucial factor in the pathogenesis of anosognosia. However, the present data may also be interpreted based on the alternative view of posterior insula as a motor association area (Mesulam & Mufson, 1985; Augustine, 1996). Consistent with that notion, the so-called "feedforward-hypothesis" suggests that the deficit leading to anosognosia might be a defect to _initiate_ movements with the paretic limb (Heilman, 1991). The patient does not intend to move and thus no mismatch between the expectancy of a movement and the perception of that movement is generated which would allow conscious perception of limb paresis.

The present data do not help to decide between "feedback" and "feedforward" hypotheses to explain anosognosia for hemiparesis. However, the data suggest that the right posterior insula is a decisive, if not the essential anatomical correlate of anosognosia for hemiparesis. This structure seems to be important for undisturbed perception of and believes about contralateral body parts.

6. Abstract

The present study investigated the incidence and diagnosis as well as the analysis of lesion location of stroke patients with anosognosia for hemiparesis or hemiplegia. These patients typically are convinced that their limbs function normally although they have obvious motor defects. Such patients may experience the paretic limbs as strange or as not belonging to them, or even attribute ownership to another person and try to push their paralyzed limb out of bed. In previous studies, the incidence of anosognosia for hemiparesis varied between 17% and 58% in samples of brain damaged patients with hemiparesis. One explanation for this wide variation might be different criteria used for the diagnosis of anosognosia. The sample of the present study consisted of 128 acute stroke patients with hemiparesis or hemiplegia. The patients were tested for anosognosia for hemiparesis using the anosognosia scale of Bisiach et al. (1986). Analysis revealed that 94% of those patients rated having "mild anosognosia", i.e. who did not acknowledge their hemiparesis spontaneously following a general question about their complaints, suffered from and mentioned other neurological deficits, such as dysarthria, ptosis, or headache. However, they immediately acknowledged their paresis when they were asked about the strength of their limbs. Obviously other deficits had a higher impact for these subjects. In fact, they had significantly milder paresis compared to patients who denied their disorder even when asked about their limbs. The data suggest that patients who do not mention their paresis spontaneously, but directly when addressed by the examiner should not be diagnosed having "anosognosia". If this more conservative cut-off criterion is applied to the data of the present as well as of previous studies, a frequency between 10% and 18% for anosognosia for hemiparesis is obtained in unselected samples of acute, hemiparetic stroke patients. The incidence of anosognosia for hemiparesis thus seems to be less frequent than previously assumed.

Previous studies have favored the idea that anosognosia for hemiparesis is related to disturbed right hemisphere processes. Here we present data supporting the hypothesis that the key area typically associated with

anosognosia for hemiparesis/-plegia is the right posterior insula. Neuronal responses in monkeys suggested that this region represents a somatosensory as well as a motor association area. Obviously signal processing in the insular cortex plays a crucial part for the generation of self-awareness and our beliefs about function of body parts.

7. References

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