Behavioral/Systems/Cognitive

Awareness of the Functioning of One's Own Limbs Mediated by the Insular Cortex?

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Normally, we are aware of the current functions of our arms and legs. However, this self-evident status may change dramatically after brain damage. Some patients with "anosognosia" typically are convinced that their limbs function normally, although they have obvious motor defects after stroke. Such patients may experience their own paretic limbs as strange or as not belonging to them and may even attribute ownership to another person and try to push their paralyzed limb out of bed. These odd beliefs have been attributed to disturbances somewhere in the right hemisphere. Here, we use lesion mapping in 27 stroke patients to show that the right posterior insula is commonly damaged in patients with anosognosia for hemiplegia/hemiparesis but is significantly less involved in hemiplegic/hemiparetic patients without anosognosia. The function of the posterior insular cortex has been controversially discussed. Recent neuroimaging results in healthy subjects revealed specific involvement of this area in the subject's feeling of being versus not being involved in a movement. Our finding corresponds with this observation and suggests that the insular cortex is integral to self-awareness and to one's beliefs about the functioning of body parts.

Key words: anosognosia; hemiparesis; somotoparaphrenia; agency; insula; spatial neglect; brain damage; human

Introduction

Normally, we are aware that our arms and legs belong to us and not someone else. When resting, we are aware that our limbs do not move, and when moving, we realize that our limbs cause the action. However, this self-evident status may change dramatically after brain damage. Some patients with anosognosia typically are convinced that their limbs function normally, although they have obvious motor defects after stroke. When asked to move the plegic or paretic arm or leg, they may do nothing or may move the limb on the opposite side. Either way, they are convinced that the plegic limb has moved appropriately. The patients may not 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 as a result of plegia of one arm). Such patients may experience their own paretic limbs as strange or as not belonging to them and may even attribute ownership to another person (somatoparaphrenia) and try to push their paralyzed limb out of bed. The mechanism underlying these false beliefs still is a matter of debate. Psychological (Guthrie and Grossman, 1952; Weinstein and Kahn, 1955) as well as neurological (Babinski, 1918; Levine, 1990; Heilman, 1991; Frith et al., 2000) theories have been put forward. Several studies found that anosognosia occurs more commonly in right- than in left-brain-

damaged patients (Nathanson et al., 1952; Cutting, 1978; Starkstein et al., 1992; Pia et al., 2004) and with large lesions involving parietal, temporal, and frontal cortices (Bisiach et al., 1986; Levine et al., 1991; Starkstein et al., 1992; Ellis and Small, 1997) (for review, see Pia et al., 2004). Subcortical lesions affecting thalamus, basal ganglia, corona radiata, capsula interna, or pons also have been reported with the disorder (Bisiach et al., 1986; Starkstein et al., 1992; Bakchine et al., 1997; Ellis and Small, 1997; Maeshima et al., 1997; Evyapan and Kumral, 1999).

In recent years, new tools of lesion mapping became available that reduce significantly the uncertainty brought in by the procedures used in previous anatomical studies and allow direct comparison with control patients (for review, see Rorden and Karnath, 2004). The present study thus reinvestigated the issue of defining the key area(s) typically associated with anosognosia for hemiplegia/hemiparesis. We performed a lesion subtraction analysis between a group of patients with anosognosia for hemiplegia/hemiparesis and a control group of stroke patients who showed the same neurological defects than the anosognosia patients, except for the critical symptom (anosognosia) to be investigated.

Materials and Methods

Clinical investigation. We selected 14 consecutively admitted acute stroke patients with right brain damage who showed anosognosia for hemiplegia/hemiparesis. In 12 of these patients, the left arm and/or leg was plegic, and many patients showed additional neurological defects such as spatial neglect, extinction, etc. (compare Table 1). 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 (anosognosia) to be investigated. We thus compared the anosognosia patients with a group of 13 right-brain-damaged acute stroke patients admitted in the

Table 1. Demographic and clinical data of all right-brain-damaged patients with hemiparesis/hemiplegia

	Anosognosia	Controls	*p* value
Number	14	13	
Sex	7 m, 7 f	8 m, 5 f	0.546
Age [median (range)]	69 (47–91)	66.5 (30–80)	0.452
Etiology	13 infarct, 1 hemorrhage	12 infarct, 1 hemorrhage	
Time since lesion (d) [median (range)]	3 (0–14)	7 (1–14)	0.293
Lesion size (% RH volume)	12.3 (5.9–36.4)	16.4 (0.3–28.8)	0.776
Paresis of contralesional side			
% present	100	100	
Arm [median (range)]	0 (0–4)	0 (0–4)	0.201
Leg [median (range)]	0 (0–4)	0 (0–4)	0.807
Somatosensory deficit of contralesional side (touch)			
% present	93	77	0.268
% t.n.p.	7	15	
Hemianopia			
% present	8	15	0.759
% t.n.p.	21	15	
Neglect			
% present	93	92	0.956
Extinction			
Visual			
% present	78	85	0.587
% t.n.p.	14	15	
Tactile			
% present	93	85	0.450
% t.n.p.	7	15	
Auditory			
% present	64	69	0.785

f, Female; m, male; t.n.p., testing not possible; RH, right hemisphere.

same period who had no anosognosia but were comparable with respect to age, acuity of lesion, size of lesion, strength of hemiplegia/hemiparesis, the frequency of sensory loss, and the frequency of additional neglect, extinction, and visual field defects (Table 1). The lesions of all subjects were demonstrated by magnetic resonance imaging (MRI) or by computed tomography (spiral CT). Patients with diffuse or bilateral brain lesions as well as patients with tumors were excluded. All patients gave their informed consent to participate in the study, which has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964).

The degree of paresis of the upper and lower limbs was scored with the usual clinical ordinal scale, where "0" stands for no trace of movement and "5" for normal movement. Scoring was performed separately for the proximal (upper arm, thigh) and for the distal (forearm, lower leg) part of each limb. Table 1 presents the averaged scores per limb. Anosognosia for hemiplegia/hemiparesis was examined using the anosognosia scale by Bisiach et al. (1986) as follows: grade 0 (no anosognosia), the disorder is spontaneously reported or mentioned by the patient after a general question about his/her complaints; grade 1, the disorder is reported only after 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 acknowledgment of the disorder can be obtained. For a firm diagnosis of anosognosia for hemiplegia/hemiparesis, only patients with grades 2 or 3 were selected (cf. Baier and Karnath, 2005) because both groups consistently do not acknowledge hemiparesis/hemiplegia even after a specific question about the strength of their limbs. Patients in the control group scored grade 0.

Visual field defects were assessed by standardized neurological examination. Spatial neglect was diagnosed when the patients showed the characteristic clinical behavior such as orienting toward the ipsilesional side when addressed from the front or the left and/or ignoring contralesionally located people or objects. In addition, the bells test was administered (Gauthier et al., 1989). This test consists of seven columns each containing five targets (bells) and 40 distracters. Three of the seven columns are on the left side of a horizontally oriented 21 × 29.7 cm sheet of paper (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 five bells within the three contralesional columns compared with the three on the ipsilesional side was considered to indicate spatial neglect. Furthermore, 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 pseudorandom order. Patients were classified as showing extinction when they reported ≥90% of the unilateral stimuli on each side correctly but failed to perceive the left stimulus during bilateral stimulation on >50% of the trials.

Lesion analysis. MRI was performed in seven stroke patients; spiral CT scanning was performed in 20 subjects. The initial scanning optionally was repeated during the following days until a firm diagnosis could be made and the infarcted area became clearly demarcated. The mean time between lesion and MRI used for the present analysis was 4.4 d (SD, 4.3) and between lesion and CT scanning was 4.3 d (SD, 2.9). The MRI protocol used diffusion-weighted (DWI) and T2-weighted fluid-attenuated inversion-recovery (FLAIR) imaging. FLAIR images provide high sensitivity for acute cerebral infarcts; DWI has proved to be particularly sensitive for the detection of hyperacute infarcts and shows high accuracy in predicting final infarct size (Brant-Zawadzki et al., 1996; Noguchi et al., 1997; Ricci et al., 1999; Schaefer et al., 2002). Scans were obtained on a 1.5 T echo planar imaging (EPI) capable system (Magnetom Sonata; Siemens, Erlangen, Germany). The FLAIR sequence was acquired with 20 axial slices (thickness, 5 mm) with an interslice gap of 1 mm, a field of view (FOV) of 175 × 220 mm^2, a repetition time (TR) of 9000 ms, and an echo time (TE) of 118 ms. DWI was performed with a single-shot EPI spin echo sequence (TR, 3200 ms; TE, 87 ms; FOV, 230 × 230 mm^2; matrix, 64 × 64 pixels; slice thickness, 5 mm; gap, 1 mm). To fit the canonical anteroposterior commissure orientation of the MRI 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. Scans were obtained on a spiral CT scanning system (Somatom Sensation 16; Siemens) that has created excitement because it provides clearer pictures with more anatomical details and in less time than previous generations of CT systems (Rorden and Karnath, 2004). Spiral CT scanning was performed with a slice sickness of 3 mm infratentorial and 8 mm supratentorial.

Being blind for the diagnosis of anosognosia, the lesions were mapped using MRIcro software (Rorden and Brett, 2000) (www.mricro.com) on slices of a T1-weighted template MRI scan from the Montreal Neurological Institute (Montreal, Quebec, Canada) (www.bic.mni.mcgill.ca/cgi/icbm_view). This template is approximately oriented to match Talairach space (Talairach and 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.

Because the two patient groups differed in sample size, we used proportional values for the MRIcro subtraction analysis. To identify the 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 [details concerning the subtraction technique in Rorden and Karnath (2004)].

Results

Figure 1A illustrates lesion density plots for each group. In both groups, lesions included the temporal and parietal cortex, the insula, and subcortically, the basal ganglia and deep white matter. To identify the structures that are specifically damaged in patients with anosognosia for hemiplegia/hemiparesis, we subtracted the superimposed lesions of the control group from the overlap image of the anosognosia group revealing a percentage overlay plot (Fig. 1B). Note that this subtraction technique codes the relative incidence of damage specific to anosognosia for hemiplegia/hemiparesis. It creates an image that only highlights regions that are both frequently damaged in patients with anosognosia as well as being typically spared in control patients. Figure 1B illustrates that the area specifically related to anosognosia for hemiplegia/hemiparesis is the right posterior insula. We found the posterior insula 62% more frequently affected in patients showing anosognosia than in controls. All of the 14 patients with anosognosia had a lesion involving this region. In contrast, we found the posterior insula affected in only five subjects from the control group. Beyond the posterior insula, additional differences between the two groups of patients were obtained in parts of the right hemisphere white matter (Fig. 1B).

Discussion

The present analysis revealed that the posterior insula is commonly damaged in patients with anosognosia for hemiplegia/hemiparesis but is significantly less involved in hemiplegic/hemiparetic patients without anosognosia who were comparable with respect to age, acuity of lesion, size of lesion, strength of hemiplegia/hemiparesis, and the frequency of additional neglect, extinction, and visual field defects.

The insula is divided by the central insular sulcus into an anterior and posterior part. The anterior part has more extensive connections with limbic, paralimbic, olfactory, gustatory, and autonomic structures. The posterior part is more closely connected to somatosensory, auditory, and motor areas (Mesulam and Mufson, 1985). The major connections of the posterior insula include those with primary and secondary somatosensory cortex (SI, SII), superior and inferior parietal lobule, orbitofrontal, prefrontal, and premotor cortex, auditory cortex (AI, AII), superior and inferior temporal cortex, as well as with the basal ganglia and thalamus (Mesulam and Mufson, 1985; Augustine, 1996).

The functional role of insular cortex still is a matter of debate. Different hypotheses have been put forward. It has been suggested that the posterior insula might represent a somatosensory association area (cf. Mesulam and Mufson, 1985; Augustine,

Figure 1. **A**, Overlay lesion plots of the patients with anosognosia for hemiplegia/hemiparesis (n = 14) and of the patients with right brain damage without anosognosia (controls; 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 and Tournoux, 1988) of each transverse section are given. **B**, Overlay plot of the subtracted superimposed lesions of the patients with anosognosia for hemiplegia/hemiparesis minus the control group. The percentage of overlapping lesions of the anosognosia patients after subtraction of controls is illustrated by five different colors coding increasing frequencies from dark red (difference, 1–20%) to white–yellow (difference, 81–100%). Each color represents 20% increments. 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.

1996). Neurons in this area showed responsiveness to auditory and to somatosensory stimulation, the latter with large receptive fields covering the limbs, trunk, or entire body (Schneider et al., 1993). Early stimulation experiments at the posterior insula reported that gross movements (Showers and Lauer, 1961) as well as restricted movements of single muscles or small groups of muscles could be elicited (Sugar et al., 1948). This led to the assumption that the insula might also be involved in motor processes. However, these latter findings lack confirmation by using more recent neurophysiological techniques. Moreover, it turned out that the insula is not an area that is typically activated during motor tasks in human imaging experiments. Lesion studies in humans further suggested that the posterior insula might be part of the human vestibular system (Brandt et al., 1994, 1995) and might be involved in language and articulation processes in the left (Dronkers, 1996; Cereda et al., 2002) and in processes of
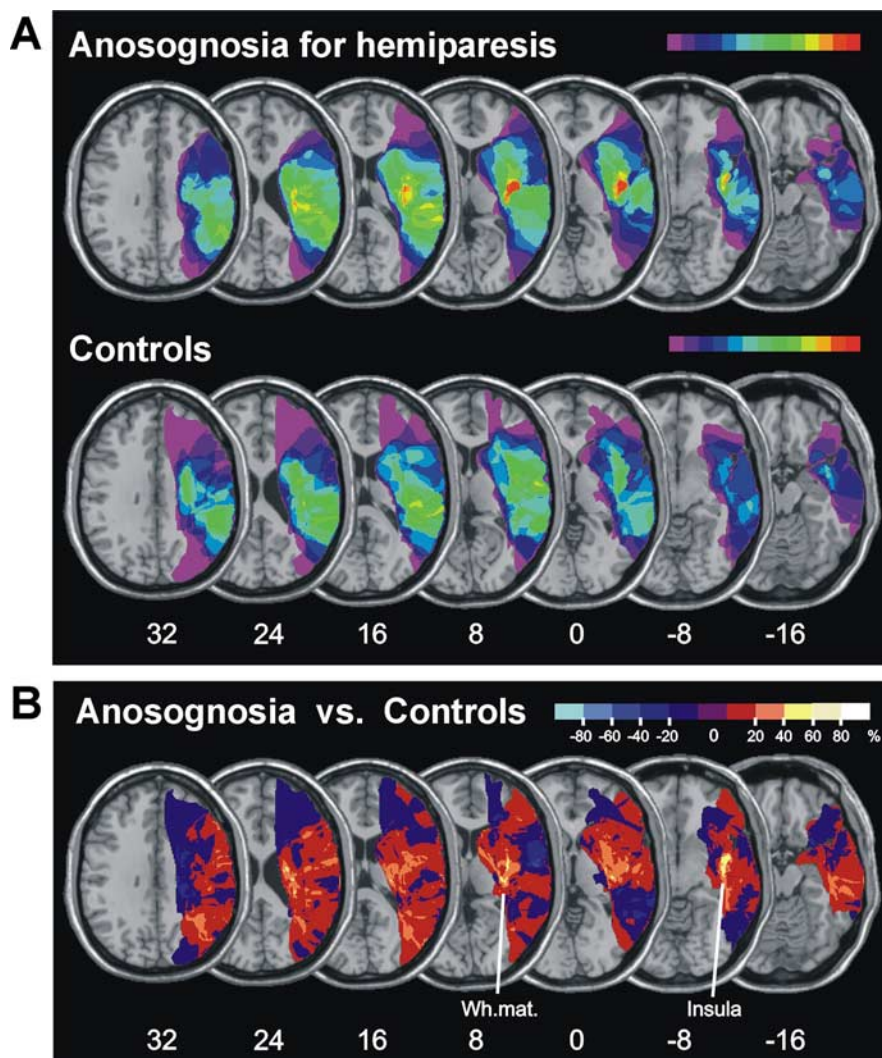
spatial exploration and orientation in the right hemisphere (Karnath et al., 2004).

In accordance with the present findings, functional imaging in healthy volunteers has revealed activity of the insula when subjects recognize aspects of themselves, suggesting a significant role in integrating different input signals related to self-awareness. Involvement of the right posterior insula was found when subjects had to indicate whether movements they saw corresponded to their executed movements or were controlled by someone else (Farrer et al., 2003). The authors observed decreased activity of the right posterior insula with a decreasing feeling of controlling the movement. The activity in the right posterior insula was low when the subjects experienced a mismatch between what they did and what they saw, whereas the activity was high when the afferent input matched to the action. Furthermore, activation in the anterior insula was found when subjects had to recognize their own face or recognize verbal descriptions of themselves (Kircher et al., 2000, 2001) or when subjects attributed an action to themselves (Farrer and Frith, 2002).

Based on the positron emission tomography (PET) results of Farrer et al. (2003) in healthy subjects, lesion of the posterior insula would be expected to disturb the feeling of being versus not being involved in a movement and may even disturb the subject's beliefs about ownership and function of body parts. It is thus striking that the present study revealed exactly this area (the posterior insula) to be significantly more lesioned in those patients who were convinced that their contralesional limbs functioned normally despite hemiplegia or hemiparesis, compared with those who did not. However, each individual lesion in our sample with anosognosia also affected structures beyond this area. Temporal and/or parietal cortex, basal ganglia, and/or deep white matter were likewise involved. The question thus arises whether evidence has been observed that a small lesion restricted to the posterior insular cortex might suffice to cause anosognosia. In fact, a recent study has reported anosognosic phenomena associated with such damage. 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 lesions. Two had right-sided and two had left-sided insular strokes. Among the two patients with right hemisphere damage, one showed somatoparaphrenia. This 75-year-old 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, not recognizing her own left upper limb. Neurological examination further revealed hypesthesia for touch and pain of the left upper extremity, alteration of graphesthesia, and stereognosis. She presented with dizziness, and her gait was insecure. Diffusion-weighted MRI revealed a right posterior insular stroke.

The conclusion that the posterior insula is significantly involved in the network integrating signals related to self-awareness and our beliefs about function and ownership of contralateral body parts is further supported by studies investigating the vestibular system. It has been observed repeatedly that caloric vestibular stimulation in patients with right brain damage using cold water in the contralesional left external ear canal induces transitory remission of anosognosia for hemiplegia/hemiparesis, including somatoparaphrenia (Cappa et al., 1987; Bisiach et al., 1991; Rode et al., 1992, 1998; Vallar et al., 2003). Interestingly, PET imaging revealed that this stimulation 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; Dieterich et al., 2003; Emri et al., 2003). Functional MRI likewise found activation of the insula with caloric or with galvanic vestibular stimulation. Suzuki et al. (2001) 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 that damage of the right posterior insula induces anosognosia for hemiplegia/hemiparesis and anosognosia related phenomena, whereas activation of this and surrounding regions induces remission of these symptoms.

To conclude, by using an unselected sample of stroke patients with and without anosognosia but otherwise comparable clinical and demographic variables, the present data suggest that the right posterior insula is an important anatomical structure related to anosognosia for hemiplegia/hemiparesis. This structure seems to be significantly involved in integrating input signals related to self-awareness and to one's beliefs about the functioning of contralateral body parts. However, it is also worth noting the limitations of the present study. First, our observation that parts of the right hemisphere white matter were more commonly affected in the anosognosia patients than in controls might point to the fact that more widespread, possibly disconnected regions of the right hemisphere contribute to the disorder. Moreover, structural MRI and CT scans might not necessarily show the full functional extent of a lesion. Areas that appear structurally intact in anatomical scans are not necessarily functioning normally, as a result of abnormal perfusion. Perfusion-weighted imaging measuring the amount and latency of blood flow that reach different regions of the brain provides a promising new method to address these questions in future research (cf. Hillis et al., 2001; Karnath et al., 2005).

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