

Asymbolia for Pain: A Sensory-Limbic Disconnection Syndrome

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We describe the behavioral and neuroanatomical features of asymbolia for pain occurring in 6 patients following unilateral hemispheric damage secondary to ischemic lesions in 5 and traumatic hematoma in 1. In the absence of primary sensory deficits, these 6 patients showed a lack of withdrawal and absent or inadequate emotional responses to painful stimuli applied over the entire body, as well as to threatening gestures. Five patients also failed to react to verbal menaces. Patients appeared unconcerned about the defect and seemed unable to learn appropriate escape or protective responses. Common associated abnormalities were rapidly resolving hemiparesis, cortical-type sensory loss, unilateral neglect, and body-schema disorders. Neuroradiological examination disclosed left hemispheric lesions in 4 patients and right hemispheric involvement in 2. Although lesion extension differed, the insular cortex was invariably damaged in all 6 patients. These findings suggest that insular damage may play a critical role in the development of the syndrome by interrupting connections between sensory cortices and the limbic system.

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Patients with asymbolia for pain (AP) can recognize pain but lack appropriate motor and emotional responses to painful stimuli applied anywhere on the body surface. They may also appear insensitive to visual threats and to verbal menaces [1-4].

In 1928, Schilder and Stengel first described this disorder in a patient with sensory aphasia and self-mutilative behavior [1]. On neuropathological examination there was a large left supramarginal gyrus infarction and additional damage involving the angular gyrus, the second frontal and first temporal convolutions, the external capsule, and the insular cortex. In a further study of 10 cases, these authors extended their clinical conception and confirmed that the lesion underlying this syndrome was mainly located in the left inferior parietal lobe [2].

Twenty-two additional cases have since been reported, but lesion location could be confirmed in only 13 [3-8]. Although AP was originally ascribed to lesions of the dominant inferior parietal lobe [1-3], the disorder has also been attributed to lesions involving other structures such as the frontoparietal cortex [6], the second somatosensory area (SII) [9], the parietal operculum, and the adjacent insular cortex [10] on either hemisphere. While Weinstein and Kahn [7] argued that AP cannot be regarded as a localizable phe-

nomenon, most of their 15 patients showed focal lesions in the frontoparietal or frontotemporal region.

Several theories have been advanced to explain the nature of the underlying functional deficit. Asymbolia for pain has been variously ascribed to abnormalities of the body-schema [11, 12], complex perceptual deficits [13], an altered relationship between body image and the awareness of pain [14], specific agnostic defects [15], and behavioral defects dependent on personality [7]. In a comprehensive review, Geschwind [10] considered AP to be secondary to a sensory-limbic disconnection and suggested that insular damage, by interrupting connections between the SII and the amygdala, might be responsible for the production of the syndrome. Although subsequent publications [8, 16, 17] are mostly in agreement with Geschwind's original formulation [10], no cases supporting this hypothesis have yet been reported.

We herewith report our findings on the behavioral and neuroanatomical aspects of AP in a prospective study involving a consecutive series of patients.

Material and Methods

From September 1985 to August 1986 a consecutive series of patients admitted to our institution because of stroke or a closed head injury were systematically evaluated for AP.

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Neurological Examination

Several abnormalities commonly associated with AP—such as transient hemiparesis, sensory loss, visual field defects, neglect, body-schema disorders, aphasia, and apraxia—were thoroughly investigated. The patients were examined by two neurologists (M. B. and R. L.) at least two times weekly during hospitalization to gather data on attitudes toward painful stimulation.

Superficial pain was assessed through pinprick and thermal stimuli applied in a single, repetitive, or prolonged way over the face, neck, trunk, limbs, and perineal region. Deep pain was tested by heavy pressure to pretibial, sternal, and supraorbital regions; passive hyperextension of fingers and toes; squeezing of calf muscles and Achilles tendons; and pinching of soft tissues on all four limbs. Motor responses (withdrawal and grimacing), emotional behavior, and autonomic reactions to noxious stimuli were examined. The responses to visual threats were also tested by presenting in either hemispace aggressive gestures, such as pretending to slap the face, punch the nose, or prick the eyes with a needle. The degree of response—whether flinch, blink, or emotional reactions—to such menacing stimuli was recorded. In addition, the extent of reaction to verbal menaces was evaluated by announcing the application of a painful stimulus, with phrases such as “I am going to pinch you hard.” Following this verbal threat, a noxious stimulus was given and the response assessed. Patients were considered to have AP only if they were alert and cooperative; had no evidence of dementia, confusion, or a previous history of psychiatric disorder; had no deficits in pain perception; and had absent or inadequate motor and emotional responses to painful stimuli applied anywhere on the body surface.

Neurophysiological Evaluation: Pain Measurements

After the patients gave informed consent, the following variables were measured: (1) *pain threshold*, defined as the minimal stimulus intensity perceived as painful; (2) *pain tolerance*, defined as the point at which the stimulus was reported to become intolerable; and (3) *pain endurance*, defined as the arithmetical difference between pain tolerance and pain threshold. Left and right arms were independently stimulated, and values from the two sides were averaged together to get the mean value. Bursts of 20 impulses/second lasting 2 seconds were delivered through two ring electrodes to the index finger. Stimuli were delivered every 3 seconds, starting at 0 mA and steadily increasing in intensity in 1-mA increments. Patients were asked to tell when they began to perceive the stimulus as painful (pain threshold) and when the stimulus became intolerable (pain tolerance). After preliminary practice, five trials in each hand were performed and the average was calculated. Statistical analysis was carried out using means, standard deviations, and Student's *t* test (two-tailed).

Neuropsychological Assessment

The following tests were administered: Wechsler Adult Intelligence Scale—revised version (WAIS-R) [18], Wechsler Memory Scale (WMS) [19], Boston Diagnostic Aphasia Examination [20] or Western Aphasia Battery [21], Token Test [22], Tactile Form Perception Test [23], Finger Localization Test [23], and Right-Left Orientation Test [23].

Neuroradiological Examination

All patients were scanned on a GE CT/T 8800. Ten consecutive slices (10-mm thick) were obtained parallel to the canthomeatal line, and several additional thin sections (2-mm thick) were made to examine lesion location and size more accurately. The involved structures were localized in a computed tomography (CT)-scan atlas [24], and the lesions were drawn on a template.

Case Report (Patient 1)

A 56-year-old right-handed man was admitted to the hospital in February 1986 because of unsteady gait and left-side weakness. Previous history was remarkable for untreated hypertension and several episodes of cardiac arrhythmia. On initial neurological examination he was alert and oriented to person and place but not to time. Digit span was four numbers forward. Cranial nerve examination demonstrated normal facial sensation, ocular motility, and visual fields, without evidence of neglect or extinction. A left-side auditory extinction was elicited only after repeated bilateral simultaneous trials. He had mild left central facial weakness and left tongue deviation on protrusion. There was a left arm pronator drift with ipsilateral hyperreflexia and left extensor plantar response. He denied weakness on the left side and insisted on returning to work. Sensation to pinprick, temperature, and deep pressure on pretibial region were normally perceived on both sides. Tactile sensation, vibration, and two-point discrimination were also bilaterally preserved, except in the distal left leg, where light touch produced only allesthetic responses. Bilateral simultaneous tactile testing over the arms revealed left-side extinction. Stereognosis, joint position sense, graphesthesia, and tactile form perception were impaired in both hands. In spite of apparently normal perception of superficial and deep pain, the patient showed a total lack of withdrawal responses. He tolerated prolonged pinprick or soft-tissue pinching in all four limbs without adequate grimacing or defensive movements of his limbs. Neither did he show any response after sternal or supraorbital pressure, thus indicating a generalized defect. Such abnormal findings were constantly recorded throughout daily evaluations of pain. On occasion, the patient willingly offered his hands for pain testing and laughed during stimulation. He had no concern about the defect and appeared highly cooperative during pain evaluation. When the patient was asked specific questions concerning his sensory and affective feelings generated by a noxious stimulus, he tended to underrate the intensity of pain and made no adverse comments. In the course of pain testing sessions he seemed unable to learn appropriate avoidance responses. Verbal and visual threats also failed to produce protective or emotional reactions. The electroencephalogram showed slowing over the right frontocentral area. A CT scan (Fig 1) revealed a lucency in the right hemisphere, consistent with an ischemic infarction, which involved the posterior insula and the adjacent anterior supramarginal gyrus (parietal operculum). Neuropsychological assessment was performed 3 weeks after onset.

The patient had a seventh-grade education. Intellectual abilities were within borderline range: on WAIS-R, he achieved a full scale of 77, with a verbal IQ of 82 and a performance IQ of 71. On WMS, his memory quotient was

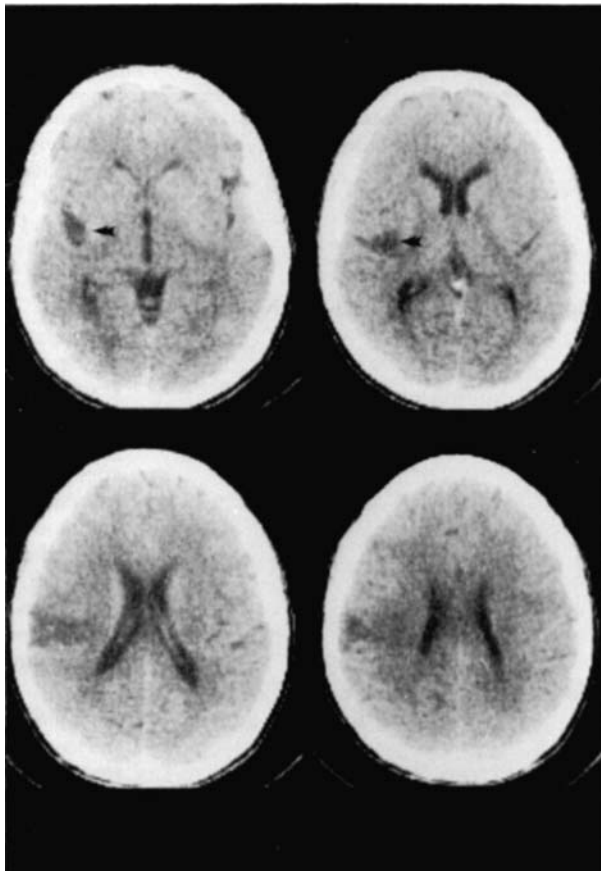


Fig 1. Computed tomography scan of a right-handed patient (Patient 1) showing an ischemic infarction involving the right posterior insula (arrows) and anterior supramarginal gyrus.

77. Language, calculation, right-left orientation, and topographical memory were all normal. In contrast, he demonstrated moderate constructional and dressing apraxia as well as impaired comprehension of affective prosody. Two months later, although hemiparesis, cortical sensory loss, neglect, and anosognosia had improved considerably, he remained unresponsive to painful stimuli and to threatening gestures or noises. At times, his lack of withdrawal threatened his safety: his wife reported that he had accidentally suffered a serious left hand burn without escape or emotional reactions. One year after the stroke the overall picture of AP remained unchanged.

Results

Demographic Data

Six patients met clinical criteria for AP. Five were men and 1 was a woman. Ages ranged from 38 to 65 years, with a mean of 54.8 years. Four were right-handed and 2 were left-handed. Educational level ranged from 7 to 14 years, with a mean of 9.1 years. Five patients (Patients 1 to 4 and 6) were evaluated within 4 weeks after stroke and the sixth (Patient 5) was first examined

1 year after the insult. Four patients (Patients 1, 2, 4, and 5) presented with a mild, rapidly resolving hemiparesis secondary to lesions on the parietal operculum and posterior insular cortex (Table 1). The other 2 patients showed moderate (Patient 6) or severe (Patient 3) hemiparesis. Both patients also had dysphagia, dysarthria, contralateral tongue deviation on protrusion, facial-oral numbness, and a severe upper and lower facial palsy. In these 2 patients the lesions involved the anterior operculoinsular region and extended into the basal ganglia. Four patients showed a cortical-type sensory loss (astereognosis, deficit in two-point discrimination and joint position sense, as well as agrophesthesia). These deficits were unilateral in 2 patients (Patients 2 and 6) and bilateral in the other 2 (Patients 1 and 3). A unilateral neglect syndrome was found in all but 1 patient. Four patients (Patients 1 to 4) showed tactile and/or visual and/or auditory extinction to double simultaneous stimulation. Patient 6 showed a moderate contralateral (left-side) multimodal neglect, and Patient 5 showed no neglect but was first examined 1 year after the brain lesion. Visual field defects were uncommon, and a right homonymous hemianopia was found in only 1 patient (Patient 5).

Although all 6 patients could adequately recognize painful stimuli and distinguish sharp from dull, all of them showed a lack of response to painful stimuli applied over the entire body. Neither superficial nor deep pain stimulation elicited a motor withdrawal, grimacing, or an appropriate emotional response. During some trials, however, fluctuations in motor performance and asymmetrical responses were occasionally noted. After prolonged deep painful stimuli, 2 patients showed a local and incomplete withdrawal response of the legs (Patients 4 and 5), while 3 patients (Patients 2, 3, and 6) showed only an incomplete unilateral defense reaction. One patient (Patient 1) not only failed to show a withdrawal response but also exhibited a reaction of "approach" to the painful stimuli (i.e., he directed his limb toward the noxious stimuli). Inappropriate emotional reactions were common: 4 patients (Patients 1, 3, 4, and 6) smiled or laughed during the pain testing procedure. This abnormal behavior ceased abruptly on discontinuing stimulation. All patients appeared quite unaware of their abnormal reactions and seemed unable to learn appropriate escape or avoidance responses. None of them became anxious or angry during the pain testing procedure; in fact, while all could recognize pain, none of them reported any unpleasant feeling. Patients showed normal autonomic reactions (tachycardia, hypertension, sweating, mydriasis) during the painful stimulation, but failed to react with flinch, blink, or adequate emotional responses to threatening gestures presented to both hemispaces. Five patients (Patients 1 to 5) also failed to react to verbal menaces.

Table 1. Clinical and Neuropsychological Features of Patients

Patient No.	Age (yr)/ Sex	Handedness	Motor Deficits	Sensory Loss	Hemianopia	Neglect	Aphasia	Other Findings
1	56/M	R	Mild, transient L hemiparesis	Cortical type, bilateral	No	Auditory, tactile L	No	Anosognosia, flat affect, aprosodia, constructional and dressing apraxia
2	42/F	L	Mild, transient R hemiparesis	Cortical type, R	No	Trimodal R	No	Anosodiaphoria, spatial dysgraphia
3	65/M	L	Severe, persistent R hemiparesis; R opercular syndrome	Cortical type, bilateral	No	Visual, tactile R	No	Anosodiaphoria, flat affect, aprosodia, left ideomotor and oral apraxia, left apraxic aggraphia, loss of dreaming
4	38/M	R	Mild, transient R hemiparesis	No	No	Visual, tactile R	Conduction	Ideational, ideomotor, and constructional apraxia; alexia; aggraphia; acalculia
5	63/M	R	Mild, transient R hemiparesis	No	Homonymous R	No	Pure word deafness	
6	65/M	R	Moderate, transient L hemiparesis; L opercular syndrome	Cortical type	No	Multimodal L	No	Anosognosia, euphoria, aprosodia, spatial dysgraphia

R = right; L = left.

Table 2. Measurements of Pain Perception and Tolerance (in milliamperes)^a

	Patients (n = 3)	Controls (n = 5)
Age (yr)	56.6 (14.4)	50.0 (14.3)
Pain threshold	5.1 (1.97)	3.9 (1.34)
Pain tolerance ^b	12.9 (3.74)	5.0 (2.0)
Pain endurance ^c	6.8 (1.68)	1.1 (.89)

^aValues represent the mean; standard deviations are shown in parentheses.

^b $p < 0.01$.

^c $p < 0.001$.

Neurophysiological Evaluation: Pain Measurements

Measurements of pain threshold, tolerance, and endurance were carried out in 3 patients (Patients 2, 3, and 6) and in 5 normal controls (Table 2). Two aphasic patients with comprehension deficits (Patients 4 and 5) and 1 patient with a severe cardiac arrhythmia (Patient 1) were not evaluated. While differences in pain threshold were not significant ($t = 1.03$, $df = 6$), patients showed significantly higher tolerance threshold ($t = 4.00$, $df = 6$, $p < 0.01$) and pain endurance values ($t = 6.44$, $df = 6$, $p < 0.001$) as compared with normal controls.

Neuropsychological Assessment

Intelligence and memory tests were administered to all patients. WAIS-R [18] scores ranged from mildly defective to normal, and low scores were obtained for the WMS [19] throughout. None of the patients showed

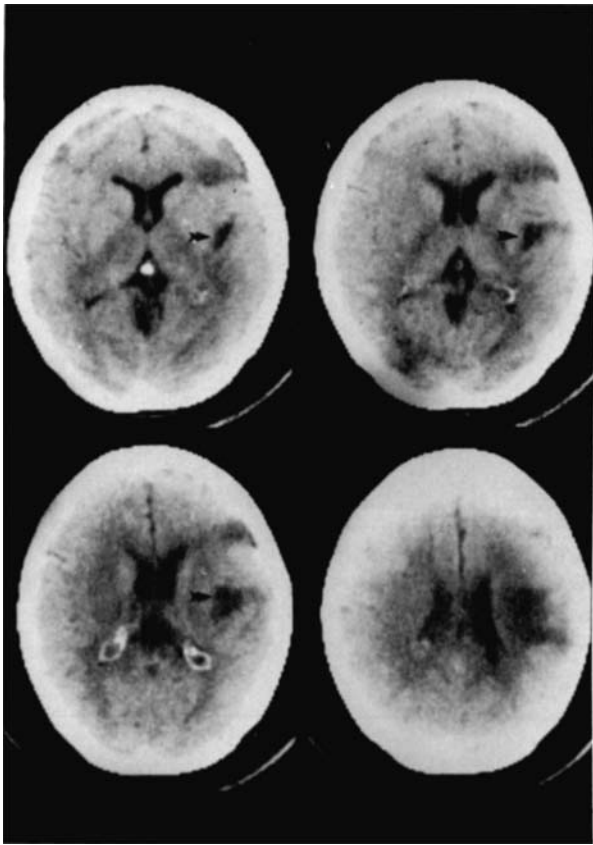


Fig 2. Computed tomography scan of a left-handed patient (Patient 2) showing an ischemic infarction involving the left posterior insula (arrows), postcentral gyrus, and white matter underlying the anterior supramarginal gyrus. Additional ischemic damage is also observed at the left frontal lobe.

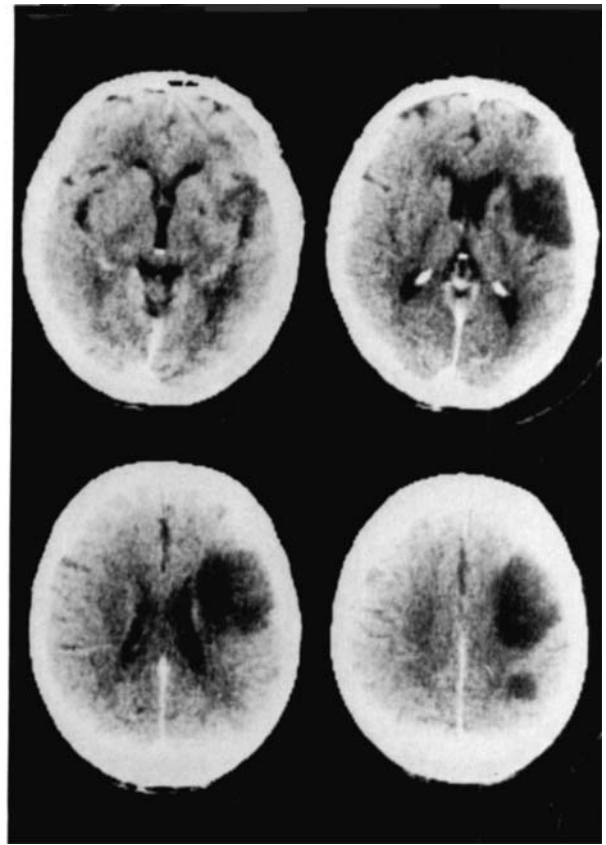


Fig 3. Computed tomography scan of a left-handed patient (Patient 3) showing an extensive ischemic infarction involving the left frontoparietal operculum, anterior insula, putamen, and anterior corona radiata. Additional ischemic damage is also seen at the left angular gyrus and left internal capsule.

deficits in the Right-Left Orientation Test [23], while 3 patients (Patients 1, 2, and 4) had low scores in the Tactile Form Perception Test [23] and 1 of them (Patient 2) achieved a low score in the Finger Localization Test [23]. One patient (Patient 4) showed a conduction aphasia, and another patient (Patient 5) showed a pure word deafness. The other 2 patients with left hemisphere lesions (Patients 2 and 3) showed no aphasia after a formal language evaluation. None of the patients with right hemisphere lesions exhibited propositional language disturbances.

Neuroradiological Examination

Whereas 5 patients had ischemic lesions in the middle cerebral artery distribution, 2 on the right hemisphere (Patients 1 and 6) (Figs 1 and 6) and 3 on the left hemisphere (Patients 2, 3, and 4) (Figs 2–4), 1 patient (Patient 5) had a left posttraumatic pseudoporencephalic lesion (Fig 5). Although lesion extension differed in each patient, the insular cortex was damaged in every patient (Fig 7). In 4 patients (Patients 1, 2, 4, and

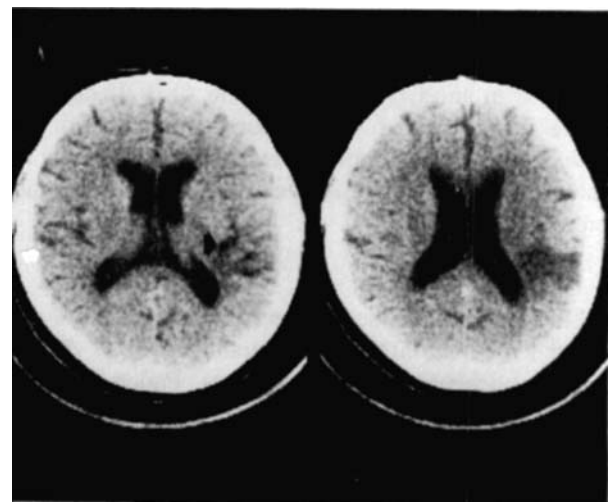


Fig 4. Computed tomography scan of a right-handed patient (Patient 4) showing an ischemic infarction involving the left posterior dorsal insula (arrow), as well as the superior temporal and anterior supramarginal gyri.

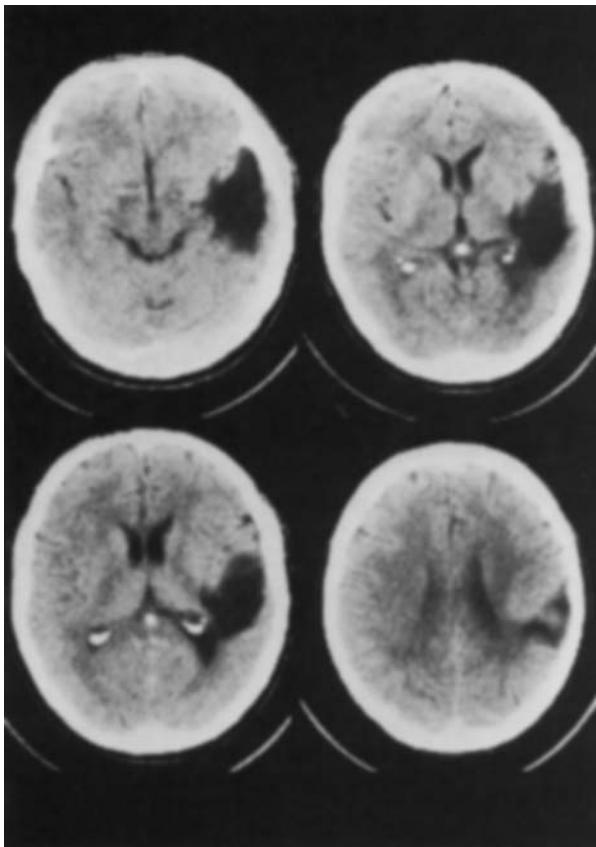


Fig 5. Computed tomography scan of a right-handed patient (Patient 5) showing a large area of low attenuation, consistent with a posttraumatic lesion, involving the left temporal lobe, posterior insula, and anterior supramarginal gyrus.

5) the lesions encroached on the posterior insula; in 1 patient (Patient 3) the lesion involved the anterior insula; and in another patient (Patient 6) it affected the entire insular cortex. In 5 patients the anterior supramarginal gyrus (parietal operculum) was partially involved, and in 3 the lesions extended into the dorso-lateral frontal lobe.

Follow-up

All but 1 patient (Patient 6) were reevaluated monthly for at least 6 months. The overall picture of AP remained unchanged in all 5 patients. Patient 3, however, was partially concerned about his condition and became fully aware and even astonished by his pathological laughter during painful stimulation. Another patient (Patient 1) suffered a serious left hand burn due to lack of proper withdrawal. In contrast, the 5 patients showed a substantial improvement in accompanying signs, particularly in hemiparesis, sensory loss, neglect, and body-schema disorders.

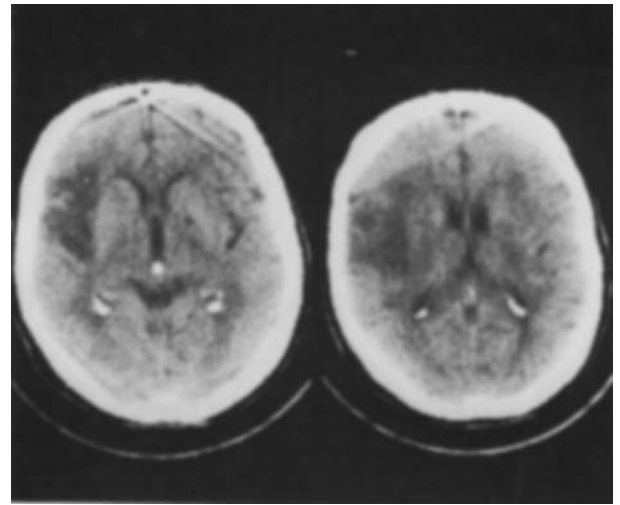


Fig 6. Computed tomography scan of a right-handed patient (Patient 6) showing an extensive ischemic infarction involving the entire right insular cortex and the adjacent frontal operculum.

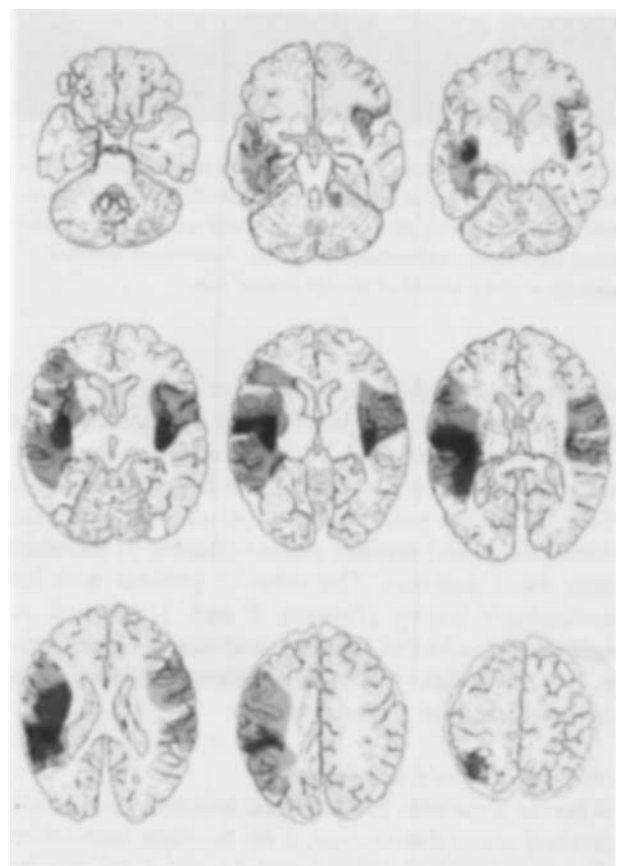


Fig 7. Template of computed tomography-scan sections showing the maximum overlap area on both posterior insular cortices.

Discussion

We described 6 patients with the clinical picture of AP. The cardinal feature was a striking modification in the appreciation of pain manifested by the lack of withdrawal to painful stimuli applied to either side of the body, together with absent or markedly attenuated emotional responses. Although there was no evidence of primary sensory defects, patients appeared unable to recognize the disagreeable nature of painful or threatening stimuli, and 5 of them also failed to react to verbal menaces. The preservation of pain perception, a critical requisite for diagnosis, was further confirmed in 3 patients through the measurement of pain threshold, which failed to reveal a significant difference between patients and a group of normal controls. As expected, all 3 patients showed significantly greater values for pain tolerance and pain endurance. The patients demonstrated a remarkably increased capacity to endure pain and to underrate the disagreeable stimulus characteristic. The high values of both psychophysical measurements recorded in these patients were consistent with the lack of aversive and normal emotional reactions to painful stimulation during the clinical assessment of pain sensation.

Common associated neurological and neuropsychological deficits were unilateral or bilateral cortical sensory loss, rapidly resolving hemiparesis, unilateral neglect, and disorders of the body-schema.

In contrast to previously reported patients [1–5, 8], other neurobehavioral deficits, such as aphasia or Gerstmann's syndrome, were not prominent findings in our patients. The paucity of such deficits might be attributed to right hemisphere dominance for language in our 2 left-handed patients with left perisylvian involvement. The remaining 2 patients with left hemisphere lesions, who were right-handed, exhibited the language disturbances traditionally described in association with AP. One of them had a conduction aphasia due to damage to posterior insula and inferior parietal lobe, closely resembling the patient reported by Potzl and Stengel [3]. The other patient suffered a traumatic hematoma, involving mainly the left temporoinsular region. Initially he developed Wernicke's aphasia, which later evolved to a pure word deafness, recalling the patient described by Hemphill and Stengel [4].

Although early authors implicated neuropsychological deficits as essential factors in the pathogenesis of AP [11–15], our findings suggest that lesion location was the most important factor associated with the development of the syndrome, as the insular cortex was invariably damaged in every patient. In fact, the development of a severe and persistent AP syndrome in 1 of our patients, following a discrete ischemic lesion in the posterior insula and parietal operculum, strongly suggests that the involvement of such structures may be sufficient for the production of the syndrome.

Although insular damage had not regularly been reported as a component of the neural basis of AP, a review of the literature revealed that in most patients the lesion location could not be properly demonstrated [5, 7, 8], while in others, clinical criteria were not clearly established [7]. On the whole, we found only 4 cases with adequate clinical descriptions and well-documented pathological data [1–3, 6]. Two patients were studied by Schilder and Stengel [1, 2]; the first had multiple areas of softening in the left hemisphere, involving the basal portion of the supramarginal gyrus, the second frontal and first temporal convolutions, the external capsule, the angular gyrus, and the insular cortex. The second patient had two expanding lesions in the left hemisphere; one of them, located in the frontal lobe, extended deeply into the caudate nucleus, the centrum semiovale, and the corpus callosum, while the other lesion infiltrated the supramarginal gyrus. Potzl and Stengel [3] reported a case of AP in which post-mortem verification showed multiple areas of softening involving the left insula, the supramarginal gyrus, and the temporal lobe. The fourth case was reported by Hecaen and de Ajuriaguerra [6], who described a patient with a large hematoma in the right hemisphere, affecting mainly the frontoparietal white matter and extending to the inferior frontal gyrus, the rolandic operculum, and the supramarginal gyrus.

There is considerable clinical and experimental evidence in the literature to support the view that the posterior insula and the parietal operculum play a leading role in somatosensory functions related to pain.

Since the SII has been considered a cortical locus for pain perception [9, 25], a lesion in this area, as a possible causal factor in some of our patients, deserves special attention. The SII has been shown to lie on the superior bank of the sylvian fissure, occupying a small portion of the parietal operculum, adjacent to the posterior insula [26–34]. Physiological studies disclosed that the neurons situated in its anterior portion are activated by tactile and pressure stimuli applied to a restricted peripheral receptive field, whereas the posterior portion has neurons with large bilateral receptive fields, responding to a variety of sensory stimuli, including pain [25–44]. In addition, Mishkin [45] suggested that the SII may act as a major link for relaying somatosensory information into the ventromedial limbic region. On the basis of 3 patients with disturbances in pain perception secondary to opercular lesions, Biemond [9] proposed that conscious pain sensation was located in the SII and suggested that damage to this region was crucial for the production of AP. However, Biemond did not consider the potential role of the insula in the production of AP, despite the presence of demonstrable insular damage in 2 of his own patients, as well as in patients previously reported [1, 3].

Although damage to the SII might explain the lack of response to painful stimuli recorded in our patients, it cannot account for the unresponsiveness to offensive visual and auditory threats. Furthermore, CT imaging revealed that the SII was spared in 2 of our patients. Thus, it seems that the overall picture of AP resulting from lesions around the central sulcus is due to predominantly insular and parietal opercular damage, rather than to SII involvement alone. Damage to the former structures is of particular interest, since it may help to interpret the behavioral pattern in terms of a sensory-limbic disconnection syndrome. Geschwind [10] speculated that AP might be considered one of the human models of such a syndrome. On discussing the underlying mechanism of AP, he suggested that damage to specific anatomical sites could account for the typical dissociation between normal pain perception and adequate emotional reaction. Geschwind even predicted that "the lesion causing pain asymbolia would in fact spare the second sensory area but involve perhaps parietal operculum and insula, cutting off the connections to the limbic system" [10].

This view is supported by new clinical and experimental evidence. We have recently reported the clinicopathological study of a right-handed patient who presented with a total lack of pain perception on the left side of the body [46]. Neuropathological examination disclosed an ischemic infarction of the right hemisphere involving the entire insula, the inner portion of the frontotemporoparietal operculum, and the underlying white matter. Although this patient clinically and pathologically resembled Biemond's patient (Patient 3 in reference [9]), SII involvement in our patient was only partial and limited to a small focus within the inner parietal opercular cortex. Pertinent neuropathological findings strongly support Mesulam and Mufson's view that damage to the posterior insula may impair the processing of noxious information by disrupting insula-amygdala connectivity [47].

Robinson and Burton have investigated in monkeys the responses of neurons belonging to the SII and neighboring areas to painful stimuli [44]. While they found a few pain-responding neurons in the SII, both the granular insula and the area 7b contained numerous neurons highly sensitive to noxious stimuli applied to either side of the body. On the basis of this experiment, they proposed that the disturbances in emotional reactions to painful stimulation observed in patients with deep parietal lesions and in patients with AP should preferentially be attributed to involvement of the lateral portion of the area 7b, rather than of the SII. Furthermore, they described a functionally distinct region within the most medial aspect of the area 7b whose neurons responded specifically to a threatening visual stimulus. Finally, their physiological observations clearly explained how a unilateral insular or

parietal opercular lesion could produce a bilateral defect in the appreciation of painful or threatening stimuli.

Mesulam and Mufson [47] demonstrated that the posterior insula is reciprocally connected with the following sensory cortices: (1) *somatosensory*—first and second somatosensory areas, areas 5 and 7b; (2) *auditory*—superior temporal cortex granular, postauditory and parainsular cortices, first and second auditory areas; (3) *visual*—medial portion of inferior temporal gyrus, as well as paramotor cortex and high-order association areas on one hand and basomedial and lateral amygdaloid nuclei on the other. Mesulam and Mufson [47] suggested that such sensory-limbic (posterior insula-amygdala) interaction is essential to appraise the affective-motivational content of perceptual experience. Thus, if this sensory link is disrupted because of damage to the insula or closely connected structures such as area 7b, patients may still be able to identify modality-specific stimuli (somesthetic, visual, or auditory) but they may fail to react with appropriate motor response or emotional tone, since they cannot attribute any significance to painful or menacing stimuli presented in these modalities. Following this interpretation, the behavior observed in most of our patients could be the result of a trimodal sensory-limbic disconnection. Alternatively, it may also be that the lesion in the insula prevents the neocortical elaboration of the limbic signal to produce appropriate neocortical cognitive and behavioral reactions to pain. Since the insula may be responsible for general alerting mechanisms to the cortex in regard to noxious stimuli, it may produce a trimodal behavioral syndrome rather than a sensory-specific behavioral syndrome. Thus, AP may be regarded as a limbic-cortical, rather than a cortico-limbic, disconnection.

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