Published in final edited form as:

Eur J Pain. 2010 May ; 14(5): 535.e1–535.11. doi:10.1016/j.ejpain.2009.10.002.

Altered pain and thermal sensation in subjects with isolated parietal and insular cortical lesions

D.S. Veldhuijzen³, J.D. Greenspan², J.H. Kim¹, and F.A. Lenz¹

¹Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, USA ²Department of Neural and Pain Sciences, University of Maryland Dental School, Program in Neuroscience, Baltimore, USA

³Division of Perioperative Care and Emergency Medicine, Rudolf Magus Institute of Neuroscience, Pain Clinic, University Medical Center Utrecht, Utrecht, Netherlands

Abstract

Studies of sensory function following cortical lesions have often included lesions which multiple cortical, white matter, and thalamic structures. We now test the hypothesis that lesions anatomically constrained to particular insular and parietal structures and their subjacent white matter are associated with different patterns of sensory loss. Sensory loss was measured by quantitative sensory testing (QST), and evaluated statistically with respect to normal values.

All seven subjects with insular and/or parietal lesions demonstrated thermal hypoesthesia, although the etiology of the lesions was heterogeneous. Cold and heat hypoalgesia were only found in the subject with the most extensive parietal and insular lesion, which occurred in utero. Cold allodynia occurred clinically and by thresholds in two subjects with isolated ischemic lesions of the posterior insular/retroinsular cortex, and by thresholds in two subjects with a lesion of parietal cortex with little or no insular involvement. Central pain occurred in the two subjects with clinical allodynia secondary to isolated lesions of the posterior insular/retroinsular cortex, which spared the anterior and posterior parietal cortex. These results suggest that nonpainful cold and heat sensations are jointly mediated by parietal and insular cortical structures so that lesions anywhere in this system may diminish sensitivity. In contrast, thermal pain is more robust requiring larger cortical lesions of these same structures to produce hypoalgesia. In addition, cold allodynia can result from restricted lesions that also produce thermal hypoesthesia, but not from all such lesions.

Keywords

Central pain; Human insula; mechanical sensation; thermal sensation; quantitative sensory testing

© 2009 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Ltd. All rights reserved.

Address all correspondence and proofs to: Fred A. Lenz, Department of Neurosurgery, Johns Hopkins Hospital, Meyer Building 8-181, 600 North Wolfe Street, Baltimore, Maryland, USA. 21287-7713, Telephone - 410-955-2257, FAX - 410-287-4480, flenz1@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Several lines of evidence suggest that the parietal and insular cortices have a role in thermal and pain perception. In subjects with lesions of these structures clinical descriptions (Cassinari and Pagni, 1969; Kenshalo, Jr. and Willis, 1991) and detailed sensory evaluations show evidence of impaired pain sensation (Boivie, Leijon, and Johansson, 1989; Greenspan et al., 2004; Greenspan and Winfield, 1992; Schmähmann and Leifer, 1992; Starr et al., 2009; Vestergaard et al., 1995). Thermal and painful stimuli can cause activation of these structures in electrophysiologic studies (Greenspan et al., 2008b; Ohara et al., 2004) and in functional imaging studies (Apkarian et al., 2005; Casey and Bushnell, 2001; Davis et al., 1998; Moulton et al., 2005). In patients with central post-stroke pain (CPSP) the lesions have often included the thalamus, other cortical regions, or white matter tracts extending below the subjacent white matter (Boivie et al., 1989; Bowsher et al., 1998; Vestergaard et al., 1995). These complex lesions complicate the interpretation of the results. For example, a posterior insular lesion which extends below the subjacent white matter into the internal capsule will disable widespread insular and parietal cortical areas, although these areas are not directly involved in the lesion. A similar lesion including part of the thalamus will disable cortical areas which cannot be identified precisely (Behrens et al., 2003). Therefore, inclusion of complex lesions, which are not anatomically constrained, could lead to confusion regarding the sensory function of the posterior insula and parietal operculum.

To our knowledge, prior reports of QST (quantitative sensory testing) in subjects with anatomically constrained, non-complex, cortical lesions of uniform pathology have been case reports of subjects with small tumors, strokes, or surgical lesions (Davis et al., 1994; Greenspan et al., 2008a; Greenspan and Winfield, 1992, 50; Ploner, Freund, and Schnitzler, 1999; Starr et al., 2009, 29; Talbot et al., 1995). These case studies are not carried out by design, but are necessitated by the difficulty in identifying series of individuals with discrete lesions of uniform pathology. These previous studies suggest that the anterior parietal cortex may be particularly important for the sensory aspect of pain. The insula may be more important for affective dimensions of pain, and for innocuous thermal sensation although the latter has not often been studied by lesion analysis (Greenspan, Lee, and Lenz, 1999).

We now examine the hypothesis that different, anatomically constrained, insular and parietal structures mediate different aspects of thermal and pain sensations. We conducted QST with individuals having brain lesions constrained to distinct parietal and/or insular cortical areas. The results demonstrate that alterations in innocuous thermal sensation are found with smaller lesions involving distinct parietal or insular cortical structures, while thermal pain perception is affected only with larger lesions spanning these structures.

METHODS

The protocols for sensory testing have been previously described (Greenspan, Ohara, Sarlani, and Lenz 2004, 109; Kim et al., 2007). These protocols conformed to the principles stated in the Declaration of Helsinki regarding the use of human subjects, and were reviewed and approved annually by the Institutional Review Boards of the Johns Hopkins University, and the University of Maryland. All subjects were identified by an arbitrary alpha-numeric code, and signed an informed consent for involvement in this protocol. Subjects included in this study were referred to Dr Lenz for assessment of CPSP (central post-stroke pain) or sensory loss, or to Dr Greenspan for QST. Cases included those with lesions involving cortex and immediately subjacent white matter, but excluded those with lesions including thalamus or caudal central nervous system structures. In the case of large lesions (Table 2, subjects E1003 and F1225) the lesions included white matter structures below a large cortical area leading to lobar lesions.

The subjects enrolled in this study were identified on the basis of radiologic anatomy from a series of 51 forebrain lesions between 1999 and 2005. All subjects had a complete neurological examination and additional somatic sensory testing with a pin, light brush, plastic bar, and metal bars either heated or cooled under a stream of tap water. Three of the subjects in this series (A0307, B1208, D1008) were diagnosed with CPSP based on clear clinical and radiologic evidence of a stroke, on evidence of altered pain and temperature sensation, and on exclusion of other causes of chronic pain. Intensity of subjects' experimental and spontaneous pain was rated using a standard VAS scale on which 0 represented no pain and 10 represented the most intense pain imaginable.

Structural Imaging Studies

MRI images (4.8 Software, 1.5 Tesla Signa Scanners, GE Medical Systems, Milwaukee, WI) of cortical structures, were taken using coronal, sagittal and axial sequences to provide a survey of the brain. All subjects were studied with MR imaging using the MRI sequences as shown in Table 2 and Figure 3. T1 weighted imaging with gadolinium enhancement was employed in the subject with a cavernoma (C0202, Table 2, Figure 2). The quality of the imaging technique improved over the period of this study, leading to variability in the MRI images (Figure 1 and Figure 2).

For cortical lesion localization standard techniques were used to identify cortical gyri and sulci from the MRI scan (Boatman et al., 1997; Lenz et al., 1998a; Vogel et al., 2003). The central sulcus was identified 1) relative to the marginal branch of the cingulate sulcus (Lenz et al., 1998b; Naidich, Valavanis, and Kubik, 1995), 2) relative to the deep symmetrical, approximately coronal sulcus on the axial scan, with a large, posteriorly convex, precentral gyral hand representation (the 'hand knob' or 'inverted omega sign'), and 3) relative to the superior and inferior frontal sulci (Naidich, 1991; Naidich, Valavanis, and Kubik, 1995). The extent of any lesion was estimated by expressing the volume of the lesion as a four-category estimate of percentage volume (0% not affected, <25% affected, 25 to 50%, >50%) of the cortical structure using a standard manual template matching technique (Table 2) (Damasio and Damasio, 1979; Mai, Paxinos, and Voss, 2007; Schaltenbrand and Bailey, 1959). The extent of each lesion was determined by two of the authors at a time when they were blind to the results of QST, which was carried out by a third author. This third author was blind to the MRI results at the time when he carried out and analyzed the results of QST.

Cortical functional mapping and neuroanatomical correlation

For subject G2303, surgical resection was planned on the basis of the MRI, and sensory, motor and language function was mapped by cortical stimulation through a grid implanted on the cortex (see Figure 3; (Uematsu et al., 1992)). The grid was composed of electrodes (2.2mm diameter) implanted in a silastic sheet in a Cartesian array, and with 1cm center to center distance between electrodes. Briefly, pulses of duration 0.3 ms and alternating polarity at 50 pulses/s were applied across pairs of adjacent electrodes in trains of 2 to 5 s duration. This technique produced excitation beneath both of the stimulated electrodes in a pair (Ranck, 1975). Stimulation mapping was carried out between electrode-pairs (bipolar stimulation). Stimulation-evoked brief movements of the face, hand or leg were classified as motor responses, and stimulation-evoked tingling sensations were classified as sensory responses. The classification of any electrode was defined to be the response that was evoked by stimulation at the both electrode pairs along the anterior posterior row of the grid which included that electrode. For example, electrode 3 along a row including electrodes 234 was classified as sensory if stimulation between electrodes 2 and 3 evoked motor and sensory responses, while stimulation between electrodes 3 and 4 stimulation evoked only a sensory response.

Surgical photographs are presented in Figure 3 (A and C) in order to put this physiological data in register with sulci and gyri as determined by the MRI (Figure 3D and E). The positions of subdural electrodes relative to the central sulcus (CS) and the sylvian fissure (SF) were determined by multiple measures. As usual, these measures included the e-SEP N20-P20 polarity reversal, results of stimulation, intraoperative observation and photographs (Crone et al., 1998; Lenz et al., 1998). E-SEP N20-P20 polarity reversal (CSe) and intraoperative pictures were consistent in terms of the location of the central sulcus.

Quantitative sensory tests (QST)

A complete neurologic history and physical examination was carried out in each case independently by a neurosurgeon and neurologist, including a detailed clinical assessment of somatic sensory function (Lenz et al., 1993). In addition, all but one of the individuals (C0202) were evaluated with QST threshold protocols, as described below. Procedures for threshold and suprathreshold determinations were as described previously (Greenspan, Ohara, Sarlani, and Lenz, 2004, 109; Kim, Greenspan, Coghill, Ohara, and Lenz 2007) (Sarlani et al., 2003), and are summarized below.

Thermal detection thresholds were derived using a feedback controlled Peltier stimulator with a 7cm² contact area (adapting temperature 33°C; Mark IX, Florida State Univ., Tallahassee, FL) or a 9cm² contact area (adapting temperature 32°C; TSA.II, MEDOC, Ramat Yishai, Israel). Because of the different adapting temperatures for the two devices, warm and cool thresholds were recorded in terms of the temperature change from baseline rather than the absolute temperature. Previous work showed negligible differences in warm and cool stimulus detectability across adapting temperatures between 30°–33°C (Rozsa et al., 1985). The thermal pain thresholds started with the probe at an adapting temperature of 35°C (for heat pain) or 30°C (for cold pain), from which the temperature increased (decreased) at a rate of 1°C per sec until the subject pressed the button or the temperature reached 50°C (0°C).

Tactile thresholds were tested using a Semmes-Weinstein monofilament kit and a classic method of limits protocol, as described previously (Essick 1992).

Tactile allodynia testing consisted of brushing with stiff brush of the type used for oil painting which exerts approximately 90 g of force. Tactile allodynia was deemed present if brush evoked sensations were described as painful or uncomfortable when applied to the affected side of the body. These stimuli were never described in such terms when applied on the unaffected side of the patients, or on either side of subjects with normal cutaneous sensitivity.

Suprathreshold thermal sensitivity testing was conducted using a protocol developed in this laboratory, which involves hand immersion into a controlled temperature waterbath (Sarlani et al., 2003). Briefly, the subject places one hand initially into an adapting bath (33°C) for a minute, and then into another bath maintained at a set temperature either higher or lower than the adapting bath. At 15 second intervals, the subject is asked to estimate (separately) the thermal intensity (how warm/hot or cool/cold), the pain intensity, and the pleasantness or unpleasantness of the sensation. This series of questions is repeated twice, and average rating is derived for each temperature, rating category, and hand.

To evaluate thermal sensitivity statistically, we referred to the mean plus or minus two standard deviations from a normative data base (MEDOC), similar to the approach of the German Neuropathic Pain Research Network (Rolke et al., 2006). Subject thresholds that fell outside that range were considered abnormal. The values tested in this way included both absolute values (e.g. the actual threshold or rating) and the difference between the affected and 'unaffected' side (side to side difference - SS). Thus, abnormal sensitivity could be determined by either extreme threshold values or by extreme laterality differences (Greenspan, Ohara,

Sarlani, and Lenz, 2004, 109; Kim, Greenspan, Coghill, Ohara, and Lenz, 2007, 27). Such an approach can identify both unilateral and bilateral sensory abnormalities. Previous work suggests that laterality differences are a more sensitive measure for unilateral sensory abnormalities (Rolke et al., 2006). For the thermal thresholds and laterality differences, normative data were taken from a database (MEDOC), which stratifies data according to sex and age (by decade). Waterbath ratings were compared to a database generated using the same protocol we have used previously (Sarlani, Farooq, and Greenspan 2003). Cold allodynia was considered present if either 1) cold pain thresholds were abnormally high (higher temperatures), or 2) ratings of cold water baths were abnormally high.

Along with QST testing at one or two body sites, qualitative testing was conducted by applying a thermode held at a fixed temperature (38°, 42°, 20°, 10°, and 46°C, in that order) to several locations on the lower and upper extremities. The subject was asked to report the quality of sensation evoked by application of the thermode. This allowed us to see the location of gross sensory abnormalities and us to determine regional variability in thermal sensitivity.

RESULTS

The results were derived from seven subjects who had either small lesions of parietal and insular cortex or large lesions spanning these cortical structures. One subject had a surgical lesion and is presented separately (Figure 3, Table S2); the other six subjects included three with strokes encompassing the posterior insula and retroinsula (A0307, B1208, D1008) (Figure 1 and 2; Table 2). One of these subjects (B1208) had a small hemorrhage into the infarct leading to a hemosiderin signal, or blooming artifact, which exaggerates the extent of the lesion. All three had transient numbness and two had transient weakness, likely related to resolving edema involving the lateral aspect of the internal capsule. A third subject with CPSP (D1008) had a substantial infarct of the posterior insula/retroinsula, as well as the frontal and parietal operculum, which spared anterior and posterior parietal cortex superior to the operculum.

Another subject (C0202) had a cavernoma involving the posterior part of the parietal operculum with less involvement of the junction of the posterior insula and retroinsula (Figure 2, column 1, row 4, sagittal image), and associated with the surrounding hemorrhagic change which is characteristic of cavernomas. This subject had infrequent simple sensory seizures (i.e. sensation without alteration of consciousness) consisting of a throbbing, burning, pins and needles pain sensation which involved the whole left side, consistent with a seizure focus in the parietal operculum (Burton, 1986; Penfield and Jasper, 1954; Williamson et al., 1992). In the absence of seizures, this person experienced no ongoing pain. Clinically, this subject had mildly reduced pin prick and light touch sensitivity on the left.

The fifth and sixth subjects had ischemic strokes one of which occurred in childhood (E1003), while the other occurred in utero (F1225). Both subjects had ischemic lesions involving the opercular, anterior and posterior parietal cortices. In one of these subjects, the lesion involved most of the retroinsula but spared most of the insula (E1003). In the other subject, the lesion involved all of the insula and retroinsula (F1225). Both lesions involved striate cortex plus associated white matter leading to a homonymous hemianopsia, and white matter pathways to the motor cortex leading to mild contralateral weakness (Table 1). In addition, the lesioned white matter contained pathways involving the areas of cortical injury. These subjects were included because adults with large strokes surveyed for this protocol had substantial medical, neurological and cognitive issues which precluded QST. The extensive sensory deficits in the subjects following strokes in utero or early in life demonstrate that sensation does not necessarily recover over long survival periods following a large stroke.

The seventh subject received a surgical lesion of the anterior parietal cortex, which was carried out for the treatment of medically intractable seizures. The subject (G2303) was a 24 year old, right handed male having both simple sensory and partial complex seizures arising from the right hemisphere. Prior to resective surgery an array of grid electrodes was implanted and used to identify the location of seizure onsets which was then resected (Figure 3); this led to a decrease in the frequency of sensory seizures. Postoperatively, he did not have clinical evidence of sensory abnormalities, or of CPSP.

The extent of the surgical resection is shown in Figure 3, as a composite of surgical photographs (Figure 3A and Figure 3C), a operative diagram (Figure 3B), and MRI scans (Figure 3D and E), with the central sulcus defined by black arrowheads. The central sulcus was identified by stimulation-evoked responses (Figure 1B), polarity reversal of the SEP, and anatomy at the time of the resection. The extent of the medial wall resection is shown in Figure 3E relative to the marginal branch of the cingulate sulcus (red arrows) and central sulcus on the operated and unoperated sides of the brain (Figure 3D and Figure 3E). The lesion involved all of leg SI and the adjacent posterior parietal cortex. Preoperative QST was precluded by the occurrence of frequent seizures.

Sensory Testing: Thresholds

All subjects were tested for thermal detection and pain thresholds which are presented in full detail in Table 2 and Table S1, while Table S3 summarizes the results to facilitate the interpretation of the results. Nonpainful warm sensations were diminished in all subjects. One subject (A0307) experienced no warmth sensation, as indicated by self-report and by the fact that the first detection of heat was at a temperature above normal heat pain thresholds. The subject with surgical resection of parietal cortex (G2303) demonstrated heat hypoesthesia bilaterally at the first postoperative time point, but only contralateral heat hypoesthesia at later time points.

Nonpainful cold sensations were also diminished or absent for all subjects tested (Table 2, Table S1 and S3). The subject with surgical resection of parietal cortex (G2303) demonstrated cold hypoesthesia bilaterally at all three postoperative time points. Subject B1208 who had a stroke of the posterior insula and retroinsula did detect cool stimuli in a normative threshold range, but described her sensation from a threshold cold stimulus as distressingly painful, and not distinctly cool.

Based on thresholds, diminished heat pain sensation was not found for any subject, although a nearly significant side-to-side difference was seen for one subject with an extensive lesion of the parietal and insular cortex (F1225, Table 2 and Table S3). This subject was also the only one demonstrating heat hypoalgesia by suprathreshold measures (see below). Subject (G2303) had normal heat pain thresholds on postoperative days 2 and 11. On postoperative day 80, his heat pain threshold was higher contralateral to the lesion, but still within the normative range. The other five subjects had threshold values that fell well within the normative range, including the other subject with an extensive parietal lesion (E1003). Therefore, heat pain hypoalgesia was significantly less common (1 of 7) than warmth hypoesthesia (6 of 6, $P=0.0047$, Fisher) or cool hypoesthesia (6 of 7, $P=0.0291$, Fisher) in this sample of subjects.

Diminished cold pain sensation was found only in subject F1225 out of six tested, based on side to side threshold differences, and suprathreshold measures. One of the other five subjects had normal cold pain thresholds, and the remaining four demonstrated cold hyperalgesia or allodynia.

Cold allodynia was observed clinically in subjects A0307 and B1208, and was confirmed by threshold and suprathreshold testing (Table 2 and Table S3). Both subjects had isolated

involvement of retroinsula and posterior insula, which may be indicative of the relationship between robust cold allodynia and this part of the brain. Cold allodynia based on QST threshold values alone was observed for the subject with a large lesion of parietal cortex (E1003), and the subject with a restricted anterior and posterior parietal surgical lesion (G2303). In the latter case the diagnosis of cold allodynia was based on side to side differences only at the third postoperative measurement. However, the interpretation of cold allodynia for this latter subject should be tempered by the fact that the change in thresholds between the second and third postoperative test sessions was due to a change in threshold on the ipsilateral side, thus leading to a significant side-to-side difference.

As measured by von Frey thresholds, deficits of tactile sensation were only found in subjects with parietal lesions (Table 2, Table S1 and S3). The subject with the surgical lesion had a transient side to side difference in von Frey thresholds (Table S1), and the subject whose parietal cortical involvement was limited to the opercular region (D1008) showed a modest threshold deficit (Table 2). The subjects with more extensive parietal cortical lesions (E1003 and F1225) showed the largest deficits. Subjects with lesions limited to posterior insular/retroinsular cortex (A0307 and B1208) did not show significant deficits in tactile threshold. These results suggest that the normal tactile detection threshold is dependent upon intact cortical structures within opercular, anterior and posterior parietal structures, but is independent of structures within the insula.

Sensory testing – Suprathreshold (waterbath) stimuli

Hypoesthesia for cold or warm temperatures, as measured by ratings during immersion of the hand in a waterbath, was found for subjects with extensive anterior and posterior parietal lesions, with (F1225) or without extensive insular involvement (E1003, Table 2). Cold and warm hypoesthesia to waterbath stimuli was not found in one subject (A0307) whose lesion was restricted to the insular cortex, despite evidence of thermal hypoesthesia based on thresholds. Therefore suprathreshold measures suggest that a larger degree of thermal hypoesthesia is found with more extensive parietal lesions.

Painful cold waterbath ratings provided evidence of hyperalgesia in subjects A0307 and E1003, and allodynia in subject B1208. These results were consistent both with their clinical criteria (A0307, B1208) and with cold pain thresholds (A0307, B1208, E1003). The distinction between allodynia and hyperalgesia in these cases is the temperature of the water that evoked pain (30°C vs. 20°C, respectively). Overall, these results demonstrate that posterior insular/retroinsular lesions in isolation (A0307, B1208) can lead to robust cold allodynia as assessed by clinical, threshold and suprathreshold measures. In the subject with a large parieto-insular lesion (F1225) significant heat and cold hypoalgesia was found by both threshold and suprathreshold measures. Heat or cold hypoalgesia were not observed in any other subject by any measure. Therefore, thermal hypoalgesia was found only in the subject with an extensive parietal and insular lesion.

CPSP Syndrome

Two subjects had CPSP with cold and tactile allodynia (Table 1 and Table S2, A0307 and B1208). A third subject had CPSP without cold or tactile allodynia (D1008). The first two subjects had lesions restricted to the posterior insula and the adjacent retroinsula while the third had a lesion encompassing the parietal operculum in addition to these structures. All three CPSP subjects used mechanical descriptors (e.g. sharp) to describe his/her spontaneous pain. Only one of these subjects (B1208) described her ongoing pain as burning pain.

The other four subjects did not develop CPSP; two of these had no (G2303), or minimal insular/retroinsular involvement (C0202). The other two had distinct involvement of anterior/posterior

parietal cortex as well as posterior insular/retroinsular cortex (E1003, F1225). Therefore, CPSP was found in cases with substantial lesions of posterior insular/retroinsular cortex (in one case including adjacent parietal operculum) in the absence of involvement of the anterior/posterior parietal cortex, but not with any case that included lesions of parietal cortex, with or without insular cortex (3/3 vs 0/4, $P=0.0286$, Fisher).

DISCUSSION

The present results demonstrate warm and cold hypoesthesia based on QST thresholds in all subjects, where data were available. The largest degree of thermal hypoesthesia was found in the subject with the largest lesion, which involved parietal and insular lobes extensively (F1225, Table S3). This is consistent with suprathreshold measures which demonstrated that sensory loss was maximal for the largest parietal lesions (E1003 and F1225). At the same time, the subject with a relatively small lesion restricted to the posterior insula and retroinsula (A0307) showed marked cool and warmth hypoesthesia, bilaterally. Therefore, these results suggest that multiple different anatomically constrained insular and parietal structures have an essential role in the expression of cold and warm sensations.

To our knowledge, this the first consecutive series of QST testing in subjects with anatomically constrained lesions of insular and parietal cortices and subjacent white matter, so that sensory function can be compared among cases (Davis, Hutchison, Lozano, and Dostrovsky, 1994; Greenspan, Coghill, Gilron, Sarlani, Veldhuijzen, and Lenz, 2008a; Greenspan and Winfield, 1992; Ploner, Freund, and Schnitzler 1999; Starr, Sawaki, Wittenberg, Burdette, Oshiro, Quevedo, and Coghill, 2009; Talbot, Villemure, Bushnell, and Duncan, 1995). Comparisons across single case studies are more limited, because the differences in the assumptions and presentation of results between cases. Therefore, the present results provide a unique perspective on structures which may be essential for thermal and pain sensation.

The present results represent a range of pathologies, which complicates the interpretation of the results. For example, inclusion of subjects with strokes in utero (F1225) and in infancy (E1003) may complicate comparisons with lesions occurring in adulthood, due to neural plasticity occurring over time following the lesion (Kaas, Merzenich, and Killackey, 1983; Nudo and Milliken, 1996). However, the residual impairment of motor and visual sensory function in adulthood after these lesions suggests that the effect of plasticity is limited after lesions early in life. Neither was there evident recovery of somatic sensory function after lesions early in life, since the subjects with the largest lesions and longest post-lesion survivals had the largest sensory deficits ((F1225, E1003 - Table S3).

A broad range of evidence demonstrates that reorganization of forebrain structures after a stroke is much more likely to cause recovery of function than further loss of function in adults and infants (Kaas, Merzenich, and Killackey, 1983; Nudo and Milliken 1996). Although strokes early in life can lead to longstanding sensory abnormalities and pain, it is unclear whether the lack of CPSP in these cases is related to the anatomy and not the pathology of the lesion (Kirton and DeVeber, 2006; Mercuri et al., 2004).

The heterogeneity of lesions included in this study might suggest that the psychophysical abnormalities could also be heterogeneous. However, thermal hypoesthesia was found in all subjects tested, regardless of pathology, and cold allodynia (based on QST thresholds) was found in four subjects. Two of these subjects with cold allodynia (A0307, B1208) had ischemic strokes of the posterior insula/retroinsula in adulthood, one with hemorrhagic conversion. One subject of the four had an extensive parietal and insular stroke in childhood (E1003), and one had a surgical lesion of anterior and posterior parietal cortex (G2303). The latter two subjects were not diagnosed with CPSP since they did not have chronic somatic pain, and since the

presence of allodynia is not sufficient to diagnose CPSP (Merskey, 1986; Treede et al., 2008). Each of these four subjects had a different type of pathology, but all had some degree of cold allodynia and cold hypoesthesia which shows that these sensory abnormalities can be expressed independent of lesion location and pathology. It should be noted that the expression of cold allodynia was different among the subjects, in terms of the thermal sensitivity range, and of a bilateral distribution in one case. This variability suggests that there are multiple mechanisms that may underlie cold allodynia, perhaps related to differences in the nature of the lesions.

Different cortical organizations underlie temperature and pain sensation

Heat hypoalgesia was found only for the subject with the largest lesion, which involved cortex and subjacent white matter of the parietal and insular lobes (F1225, Table S3). This is congruent with thalamic studies demonstrating that heat hypoalgesia only occurs with an extensive lesion of the thalamic nucleus Vc (Kim, Greenspan, Coghill, Ohara, and Lenz, 2007; Montes et al., 2005). The present results are consistent with the cortical projection pattern of Vc and the nuclei behind Vc (Burton, 1986), and with the widespread cortical activations which occur in response to painful heat stimuli (Apkarian et al., 2005; Casey and Bushnell, 2001). These results suggest that, unlike innocuous thermal sensation, heat pain perception is mediated by a multiple independent structures, so that a lesion of one structure can be compensated for by the intact structures within either parietal or insular cortex.

Bilateral sensory abnormalities

Bilateral thermal hypoesthesia was observed in this series: (Table 2 and Table S1) for cold in two subjects (A0307, G2303), and for warm in three (A0307, B1208, D1008). Bilateral sensory effects of unilateral lesions have been described previously in small subsets of central pain cases (Casey and Bushnell, 2001; Vestergaard et al., 1995), although alternative explanations for bilateral effects must be considered.

Of the cases in the current study, A0307 may have an alternative basis for a bilateral hypoesthesia based on his diabetes and advanced age. In this case, evidence of peripheral neuropathy was not found during the clinical exam, nor was there any proximal-distal gradient of thermal sensitivity seen with qualitative sensory testing (see Methods: QST) (Adams, Victor, and Ropper, 1996). Even though D1008 showed warm hypoesthesia bilaterally, there was a significant side-to-side difference, revealing a greater contralesional effect. None of the other subjects had evidence of peripheral neuropathy, as judged by the absence of predisposing conditions (diabetes, alcoholism, auto-immune diseases, vitamin deficiency), and the lack of a qualitative proximal-distal gradient in thermal sensation on the extremities. Nevertheless, the possibility that bilateral sensory loss results from unilateral lesions must be interpreted with caution.

Central Pain

In this study, it is clear that physiologic abnormalities of cold sensation were independent of both the pathology of the lesion, and the occurrence of CPSP (Boivie et al., 1989; Ohara et al., 2004; Vestergaard et al., 1995). CPSP occurred only in individuals with lesions including posterior insula/retroinsula, but sparing the anterior and posterior parietal cortex in all cases (A0307, B1208, D1008). It is difficult to draw anatomic conclusions from these cases of CPSP since all three occurred in subjects with ischemic stroke, while none occurred in subjects with lesions of other pathologies. Lesions of parietal and insular lobes resulting in CPSP have been identified in previous studies, although it is unclear whether these studies included lesions constrained to insular or parietal cortex (Andersen et al., 1995; Bowsher et al., 1998; Leijon et al., 1989).

Evidence from neuroimaging studies suggests that the parietal lobe is involved in the mechanism of CPSP and CPSP-associated allodynia in subjects with strokes of the lateral medulla (Wallenberg syndrome), and the thalamic nucleus Vc (Kim, Greenspan, Coghill, Ohara, and Lenz; 2007; Peyron et al., 1998). In both studies a combined cold and mechanical cutaneous stimulus produced allodynia, and was associated with intense blood flow activation of contralateral sensorimotor (frontal and parietal) cortex. In addition, pain sensations are evoked in subjects with CPSP by electrical stimulation of S1 cortex (Brown and Barbaro, 2003; Katayama, Tsubokawa, and Yamamoto, 1994; Nguyen et al., 2000). Lesions of parietal cortex can dramatically relieve pain in subjects with CPSP resulting from thalamic lesions (Canavero and Bonicalzi, 2007; Helmchen et al., 2002; Soria and Fine, 1991). In combination with these results the present results suggest the testable hypothesis that CPSP can result from lesions of the posterior insula or retroinsula which spare anterior and posterior parietal cortex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health □ National Institute of Neurological Disorders and Stroke (NS38493 and NS40059 to FAL NS-39337 to JDG). We thank C. Cordes and L. H. Rowland for excellent technical assistance.

REFERENCES

- Adams, RD.; Victor, M.; Ropper, AH. Principles of neurology. New York: McGraw-Hill; 1996.
- Andersen P, Vestergaard M, Ingeman-Nielsen M, Jensen TS. Incidence of central post-stroke pain. *Pain* 1995;61:187–193. [PubMed: 7659428]
- Apkarian AV, Bushnell MC, Treede RD, Zubieta KB. Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain* 2005;9:463–484. [PubMed: 15979027]
- Behrens THE, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat. Neurosci* 2005;6(7):750–757. [PubMed: 12808459]
- Boivie, J. Central pain. In: Wall, PD.; Melzack, R., editors. *Textbook of pain*. Edinburgh: Churchill Livingstone; 1999. p. 879-914.
- Boivie J, Leijon G, Johansson I. Central post-stroke pain--a study of the mechanisms through analyses of the sensory abnormalities. *Pain* 1989;37(2):173–185. [PubMed: 2748190]
- Bowsher D, Leijon G, Thuomas KA. 1998. Central poststroke pain: correlation of MRI with clinical pain characteristics and sensory abnormalities. *Neurology* 1989;51(5):1352–1358. [PubMed: 9818859]
- Brown JA, Barbaro NM. Motor cortex stimulation for central and neuropathic pain: current status. *Pain* 2003;104(3):431–435. [PubMed: 12927615]
- Burton, H. Second somatosensory cortex and related areas. In: Jones, EG.; Peters, A., editors. *Cerebral Cortex, Vol 5 Sensory-Motor Areas and Aspects of Cortical Connectivity*. New York and London: Plenum Press; 1986. p. 31-98.
- Canavero, S.; Bonicalzi, V. *Central Pain Syndrome: Pathophysiology, diagnosis and management*. NY, NY: Cambridge Press; 2007.
- Casey, KL.; Bushnell, MC. Seattle. Washington: IASP press; 2001. *Pain imaging*.
- Cassinari, V.; Pagni, CA. *A neurosurgical survey*. Cambridge, Massachusetts: Harvard University Press; 1969. 1969. *Central Pain*.
- Crone NE, et al. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. *Brain* 1998;121:2271–2299. [PubMed: 9874480]
- Davis KD, Hutchison WD, Lozano AM, Dostrovsky JO. Altered pain and temperature perception following cingulotomy and capsulotomy in a patient with schizoaffective disorder. *Pain* 1994;59(2): 189–199. [PubMed: 7892016]

- Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 1994;80(3):1533–1546. [PubMed: 9744957]
- Essick GK. Comprehensive clinical evaluation of perioral sensory function. *Oral. Maxillofac. Surg. Clin. North. Am* 1992;4:503–526.
- Greenspan JD, Coghill RC, Gilron I, Sarlani E, Veldhuijzen DS, Lenz FA. Quantitative somatic sensory testing and functional imaging of the response to painful stimuli before and after cingulotomy for obsessive compulsive disorder (OCD). *European Journal of Pain* 2008a;12:990–999. [PubMed: 18328752]
- Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasyllian cortex. *Pain* 1999;81(3):273–282. [PubMed: 10431714]
- Greenspan JD, Ohara S, Franaszczuk P, Veldhuijzen JS, Lenz FA. Cold stimuli evoke potentials can be recorded directly from parasyllian cortex in humans. *J. Neurophysiol* 2008b;100:2282–2286. [PubMed: 18579655]
- Greenspan JD, Ohara S, Sarlani E, Lenz FA. Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. *Pain* 2004;109(3):357–366. [PubMed: 15157697]
- Greenspan JD, Winfield JA. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 1992;50(1):29–39. [PubMed: 1513603]
- Helmchen CM, Lindig D, Petersen D, Tronnier V. Disappearance of central thalamic pain syndrome after contralateral parietal lobe lesion: implications for therapeutic brain stimulation. *Pain* 2002;98(3):325–330. [PubMed: 12127034]
- Kaas JH, Merzenich MM, Killackey H. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. *Annu. Rev. Neurosci* 1983;6:325–356. [PubMed: 6340591]
- Katayama YT, Tsubokawa T, Yamamoto T. Chronic motor cortex stimulation for central deafferentation pain: experience with bulbar pain secondary to Wallenberg syndrome. *Stereotact. Funct. Neurosurg* 1994;62(1–4):295–299. [PubMed: 7631085]
- Kenshalo, DR.; Willis, WD, Jr. The role of the cerebral cortex in pain sensation. In: Peters, A.; Jones, EG., editors. *Cerebral Cortex, Vol 9 Normal and Altered States of Function*, 153–212. London: Plenum Press; 1991. p. 153–212.
- Kim JH, Greenspan JD, Coghill RC, Ohara S, Lenz FA. Lesions limited to the human thalamic principal somatosensory nucleus (ventral caudal) are associated with loss of cold sensations and central pain. *J. Neurosci* 2007;27:4995–5004. [PubMed: 17475808]
- Kirton A, DeVeber G. Cerebral palsy secondary to perinatal ischemic stroke. *Clin. Perinatol* 2006;33:367–386. [PubMed: 16765730]
- Leijon G, Boivie J, Johansson I. Central post-stroke pain-neurological symptoms and pain characteristics. *Pain* 1989;36:13–25. [PubMed: 2919091]
- Lenz FA, Rios M, Chau D, Krauss GL, Zirh TA, Lesser RP. Painful stimuli evoke potentials recorded from the parasyllian cortex in humans. *J. Neurophysiol* 1998;80(4):2077–2088. [PubMed: 9772262]
- Lenz FA, Seike M, Richardson RT, Lin YC, Baker FH, Khoja I, Jaeger CJ, Gracely RH. Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *J. Neurophysiol* 1993;70(1):200–212. [PubMed: 8360716]
- Mercuri E, et al. Neonatal cerebral infarction and neuromotor outcome at school age. *Pediatrics* 2004;113(1 Pt 1):95–100. [PubMed: 14702455]
- Merskey H. Classification of chronic pain. *Pain* 1986;S1–S220.
- Montes CM, Magnin J, Maarrawi M, Frot, Convers P, Mauguier F, Garcia-Larrea L. Thalamic thermo-algesic transmission: ventral posterior (VP) complex versus VMpo in the light of a thalamic infarct with central pain. *Pain* 2005;113(1–2):223–232. [PubMed: 15621383]
- Moulton EAM, Keaser L, Gullapalli RP, Greenspan JD. Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. *J Neurophysiol* 2005;93(4):2183–2193. [PubMed: 15601733]
- Naidich TP. MR imaging of the brain surface anatomy. *Neuroradiology* 1991;33:S95–S99.

- Naidich TP, Valavanis AG, Kubik S. Anatomic relationships along the low middle convexity: part 1- normal specimens and magnetic resonance imaging. *Neurosurg* 1995;36:517–532.
- Nguyen JP, Lefaucheur JP, Le Guerinel C, Eizenbaum JF, Nakano N, Carpentier A, Brugieres P, Pollin B, Rostaing P, Keravel Y. Motor cortex stimulation in the treatment of central and neuropathic pain. *Arch. Med. Res* 2000;31(3):263–265. [PubMed: 11036176]
- Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J. Neurophysiol* 1996;75(5):2144–2149. [PubMed: 8734610]
- Ohara S, Crone NE, Weiss N, Treede RD, Lenz FA. 2004. Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. *J. Neurophysiol* 2004;91(6): 2734–2746. [PubMed: 14602841]
- Ohara, S.; Weiss, N.; Hua, S.; Anderson, WS.; Lawson, HC.; Greenspan, JD.; Crone, NE.; Lenz, FA. Allodynia due to forebrain sensitization demonstrated by thalamic microstimulation. In: Brune, K.; Handwerker, HO., editors. *Hyperalgesia: molecular mechanisms and clinical implications*. Seattle: IASP Press; 2002.
- Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston: LittleBrown. 1954
- Peyron R, Garcia-Larrea L, Gregoire MC, Convers P, Lavenne F, Veyre L, Froment VC, Mauguier F, Michel D, Laurent B. Allodynia after lateral-medullary (Wallenberg)infarct: a PET study. *Brain* 1998;121:345–356. [PubMed: 9549510]
- Ploner M, Freund HJ, Schnitzler A. Pain affect without pain sensation in a patient with a postcentral lesion. *Pain* 1999;81:211–214. [PubMed: 10353510]
- Ranck JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res* 1975;98:417–440. [PubMed: 1102064]
- Rolke R, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123(3):231–243. [PubMed: 16697110]
- Rozsa AJ, Molinari HH, Greenspan JD, Kenshalo DR Sr. The primate as a model for the human temperature-sensing system: 1. Adapting temperature and intensity of thermal stimuli. *Somatosens. Res* 1985;2(4):303–314. [PubMed: 4035150]
- Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. *Pain* 2003;106(1–2):9–18. [PubMed: 14581105]
- Schmahmann JD, Leifer D. Parietal pseudothalamic pain syndrome: clinical features and anatomic correlates. *Arch. Neurol* 1992;49(10):1032–1037. [PubMed: 1417510]
- Soria ED, Fine EJ. Disappearance of thalamic pain after parietal subcortical stroke. *Pain* 1991;44:285–288. [PubMed: 2052398]
- Starr CJ, Sawaki L, Wittenberg GF, Burdette JH, Oshiro Y, Quevedo AS, Coghill RC. Roles of the insular cortex in the modulation of pain: insights from brain lesions. *J Neurosci* 2009;29(9):2684–2694. [PubMed: 19261863]
- Talbot JD, Villemure JV, Bushnell MC, Duncan GH. Evaluation of pain perception after anterior capsulotomy: a case report. *Somatosens. Mot. Res* 1995;12(2):115–126. [PubMed: 7502602]
- Treede RD, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70(18):1630–1635. [PubMed: 18003941]
- Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive unselected patients with central post-stroke pain. *Pain* 1995;61:177–186. [PubMed: 7659427]
- Williamson PD, et al. Parietal lobe epilepsy: diagnostic considerations and results of surgery. *Ann. Neurol* 1992;31(2):193–201. [PubMed: 1575458]

Figure 1.

MR images of the two subjects with lesions limited to the insula/retroinsula. The details of the MRI technique are given in the top rows of Table 2. The three coronal images were chosen to be approximately at the level of the anterior insula (left), the posterior insula (middle), and the section showing the largest extent of the lesion (right). The sagittal and horizontal images were chosen to best reveal the pathology. Small white arrowheads indicate the central sulcus.

Figure 2.

MR images of four subjects who demonstrated lesions involving both insula and parietal cortex. The first row shows the anterior insula, the second row shows the posterior insula or retroinsula. The third row is a coronal section showing the lesion at its largest as follows: D1008 is at 75% of the distance from the AC to the PC, C0202 junction of insula and retroinsula, E1003 is 33% of the distance from anterior to posterior insula, and F1225 is behind PC by approximately $\frac{1}{2}$ the ACPC distance. The fourth row consists of sagittal images through the opercula for columns one and two, and through the insula in 3 and 4. The fifth row shows the axial image chosen to reveal the largest extent of the lesion in relation to the insula.

Figure 3.

Operative photographic and MRI images of the brain. Photographs at the level of the central sulcus were taken during the grid implant (panel 3A), and after the resection (panel 3C). The orientation of panels A to C is indicated by the letters in panel A: A anterior, P posterior, L left (medial), R right (lateral). The black arrowheads indicate the central gyrus which forms a convex posterior structure, the 'hand knob' of motor cortex (see text). Panel 3B shows the results of physiologic mapping relative to the veins and the central sulcus (small anterior vein) and the post central sulcus (large posterior vein), which are also seen in the photographs. This combination of these images allows us to present the location of sites where electrical stimulation evoked tingling sensations (blue circles) and motor effects (tetanic contractions,

red circles, panel 3B) and pial resection margins (Panel 3C). The surgical findings (Figure 3C) are explained in the text.

Table 1

Clinical features of subjects.

	A0307	B1208	D1008	C0202	E1003	F1225
Sex/ age at onset/age at sensory test/handedness	M/65/77/R	F/41/43/R	M/51/52/R	M/30/33/R	F/2/33/R switched to L after stroke	M/prenatal/20/L
Lesion Dx/lesion side	Infarct/ L	Infarct/ R	Infarct/ L	Cavernoma (3cm) /R;3 cavernomas (<5mm)/ L	Childhood infarct/L	Infarct in utero/L
Stroke history and symptoms	Transient R sided numbness.	Transient slurred speech, dysarthria, arm & leg weakness, numbness.	Transient arm weakness and numbness.	L hand feels "numb" and "bothersome".	R sided non-disabling weakness and sensory loss at 2 years after meningitis.	R sided visual loss and non-disabling weakness.
Pain classification	CPSP	CPSP.	CPSP.	No chronic pain.	No chronic pain	No chronic somatic pain
Intercurrent illness	NIDDM.	Migraine.	HBP, Meniere's, cervical Spondylosis with neck pain.	Simple Sz characterized by numbness & tingling.	Simple motor Sz (R arm), IBS.	Epilepsy, IBS.
Clinical neurologic (non-somatic sensory) exam at time of QST.	Normal	Slight pronator drift, Otherwise Normal.	Normal.	Normal.	R HH. Face, arm weak strength and increased reflexes.	R HH, mild weakness (5-of LE and UE muscles.
Clinical somatic sensory exam, at time of quantitative testing.	Intact: light touch, cool, graphesthesia, position.	Mildly decreased pinprick, and light touch; cold allodynia; arm & leg.	Normal.	Mildly reduced pin prick and light touch sensitivity on the left side, including face, hand & foot.	Absent light touch & pinprick, cold feels hot throughout hemibody Mosquito bite described as itch only.	Decreased light touch, warm and cool, hemibody, but most pronounced on arm.

AC+PC: anterior+posterior commissure, CAD: coronary artery disease, DTR: deep tendon reflexes, Dx: diagnosis, F: female, HH: homonymous hemianopsia, HBP:hypertension, IBS: irritable bowel syndrome, L: left, M: male, MidC: midcommissural point, MMSE: Mini-mental status, ML: midline, NA: not available, NIDDM: non-insulin dependent diabetes, R: right, Sz: seizures, Simple Sz: a seizure not associated with an alteration of consciousness.

Table 2

Results of lesion localization and quantitative sensory testing

Subjects	A0307	B1208	C0202	D1008	E1003	F1225
MRI sequences						
Coronal, sagittal, axial (voxel size in mm)	T1, T1, T1 (5×5×3)	T1+Gad, T1+Gad, T1+Gad (5×5×5)	T1, T1, T1 (5×5×5)	Flair, Flair, T2 (5×5×5)	T1, T1, T2 (1.5×5×5)	T1, T1, Flair (1.5×3×5)
Extent of brain lesion (%)						
Anterior insula	0	0	0	<25	0	>50
Posterior insula	25–50	25–50	<25	25–50	0	>50
Retoinsula	25–50	<25	<25	<25	<25	>50
Parietal operculum	0	0	25–50	>50	>50	>50
Anterior-posterior parietal cortex	0	0	0	0	>50	>50
Thermal thresholds (affected vs control)/(bold = abnormal)/(side to side diff = SS+, otherwise blank)						
Test site	Forearm	Hand and foot	Hand	Forearm	Thenar	Forearm
Cold detection (ΔT, °C)	-9.5 vs -10.3	-2.0 vs -1.2 (hand) [#] -2.4 vs -9 (foot) [#]	-15.0 vs -1.6; SS+	-6.0 vs -2.3; SS+	-3.7 vs -1.0; SS+	<-15.0 vs -1.2; SS+
Cold pain (°C)	16.3 vs 10.4; SS+	29.2 vs 9.6 (hand); 29.9 vs 13.3 (foot); SS+	N/A	<4 [§]	22.9 vs 14.0; SS+	2.6 vs 14.4; SS+
Heat detection (ΔT, °C)	>+15.0 vs +13.0	+4.4 vs +4.5 (hand) +7.0 vs +5.7 (foot)	N/A	+5.7 vs +3.7 SS+	+7.8 vs +1.4; SS+	+15.2 vs +2.4; SS+
Heat pain (°C)	>50 vs 47.6	42.5 vs 43.1 (foot)	47.2 vs 48.9	50 vs 49.8	48.3 vs 44.1	48.5 vs 42.9
Mechanical thresholds (affected vs control)						
Test site	Calf	Hand	Hand	Forearm	Forearm	Forearm
von Frey (gm)	0.513 vs 0.528	0.030 vs 0.0073	N/A	0.45 vs 0.138; SS+	1.40 vs 0.021; SS+	2.80 vs 0.027; SS+
Tactile allodynia	Yes	Yes*	No	No	No	No
Waterbath sensory ratings (0–10 scale; affected vs control)						
Cool sensation (25°C)	8.0 vs 6.5	Pain reported at all cold temperatures	N/A	N/A	0 vs 6.0; Hypoesthesia	3.7 vs 7.2; Hypoesthesia
Cold pain (20°C)	6.0 vs 6.0; Hyperalgesia (bilateral)	10 vs 0. (at 30°C instead of 20°C); Allodynia	9.4 vs 10.8 (withdrawal latency in sec at 1°C)	N/A	6.5 vs 1.0; Hyperalgesia	1.8 vs 5.0; Hypoalgesia
Warm sensation (37°C)	5.5 vs 6.0	4.5 vs 5.5	N/A	N/A	0 vs 6.0; Hypoesthesia	1.8 vs 4.2; Hypoesthesia

Subjects	A0307	B1208	C0202	D1008	E1003	F1225
Heat pain (44°C and/or 47°C)	0 vs 0 (44°C) ; 10 vs 10 (47°C)	10 vs 9.5 (44°C); Hyperalgesia (bilateral)	N/A	N/A	0 vs 0 (44°C) ; 10 vs 10 (47°C)	0 vs 8.5 (44°C); Hypoalgesia

Extent of the brain lesion is presented as an approximate percentage of the structure involved. The results of sensory testing within each cube of the table indicate the data derived from the affected body side (contralateral to the lesion) versus the control side. For the section on thermal thresholds bold text indicates a value outside of the normative range. For warm and cool detection thresholds, the values are in terms of changes from the baseline temperature of 32 or 33°C (see text). Significant side to side differences are indicated by 'SS+' and two thresholds in bold without SS+ indicates bilateral sensory loss.

For the waterbath sensory rating, values are presented with reference to a 0–10 scale. Subject D0202 was only tested for cold pain tolerance, and the values presented are the times to withdrawal from the waterbath.

Abbreviations: N/A; not assessed.

Cold detection threshold sensation was a burning pain, not coolness.

* Brushing was nonpainful, but punctuate (von Frey) probes were painful.

§ Not painful at the minimum temperature of 4°C bilaterally.