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Psychophysical and Cerebral Responses to Heat Stimulation in Patients with Central Pain, Painless Central Sensory Loss, and in Healthy Humans

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INTRODUCTION

Some patients with central nervous system (CNS) lesions suffer chronic pain that appears at variable times following the onset of the CNS lesion. Various estimates indicate that 8 - 18% of patients with ischemic stroke, 30% of patients with multiple sclerosis, and 34% of patients with spinal cord injury experience pain attributable to the CNS lesion and therefore referred to as central pain (CP). CP is also recognized as a complication of Parkinson's disease, with an incidence of approximately 10% [4]. Comprehensive reviews of various aspects of CP have appeared recently [95, 8, 101, 113, 19, 45, 55].

Nearly all patients with CP experience pain within an area of reduced pain and temperature sensation; this appears to be largely independent of the location or type of lesion although tumor-related CP appears to be rare [59, 9, 105, 93, 14, 19]. Typically, the pain is constant but modulated by mood and environmental factors. Many patients with CP experience allodynia or hyperalgesia within the area of sensory loss and pain. These observations suggest that an impairment of functions mediated through the spinothalamic tract causes an increase of resting and evoked activity within central nociceptive pathways [28]. However, a loss of thermal and nociceptive sensory function, although perhaps necessary, is not sufficient for the development of CP because most patients with this type of sensory loss do not develop CP [49]. Direct recordings and stimulation within the somatosensory thalamus suggest that long-term changes in excitability have occurred [61, 42, 46, 60] and functional imaging studies have shown exaggerated thalamic and cortical neurovascular responses in

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patients with CP [29, 80, 54]. A sample of CP patients with focal cerebral infarctions showed a widely distributed loss of brain opioid receptor binding capacity that included the thalamus and several pain-activated cortical areas, suggesting either opioid receptor loss or increased receptor occupancy [118]. Nonetheless, a neurophysiological basis for the pain of CP remains unknown [49, 12, 35, 19].

The observations cited above suggest that CP develops because of unique changes in the excitability of some central structures and pathways that process nociceptive and thermal information. Therefore, we investigated the magnitude and distribution of activation intensity changes in a sample population of healthy individuals, patients with focal CNS lesions and a painless loss of pain and heat sensation, and patients with CP. We used contact heat stimuli below and above the noxious range and measured a normalized estimate of the change in regional cerebral blood flow (rCBF) from the resting condition. We examined group differences in both resting and stimulus-evoked activity. Because these measurements require estimates of baseline activity that are temporally more stable than functional magnetic resonance imaging [98, 119], we used positron emission tomography (PET) with intravenous $H_2^{15}O$ as the tracer.

METHODS

Participants

The demographic and relevant clinical characteristics of all participants are shown in Table 1. Basic eligibility for participation required that each participant be within the age range of 40 to 70 years, able to communicate fluently in English, and sign informed consent documents approved by the Internal Review Boards of the Medical Centers of The University of Michigan and The Veteran's Affairs Medical Center, Ann Arbor. In summary, we recruited a healthy control (HC) group of 15 males ages 42 to 64 years, 10 patients with central pain (CP) ages 48 to 66 years, and 10 patients, ages 40 to 68 years, with central nervous system (CNS) lesions but no pain (NP). We recruited HC participants through newspaper and poster notifications placed at the Veteran's Affairs Medical Center (VAMC Ann Arbor) and at the University of Michigan Medical Center. For the HC group, these notifications specified the required age range and that each participant should be pain free, in excellent general health, without a history of neurological disease, and not taking analgesic or psychoactive medication. We also used newspaper and poster notifications to recruit patients in both the CP and NP groups; these notifications were similar to those used for the HC group but specified that a neurological diagnosis of brain or spinal cord damage was required for participation in the study. In addition, patients attending the Neurology Clinic at the Ann Arbor VAMC were informed of the opportunity to participate in the study if their history and examination was consistent with eligibility. Eligibility for participation in the CP and NP groups included clinical evidence for a single, localized CNS lesion resulting in a unilateral impairment of nociceptive sensation detectable on the neurological examination; we excluded volunteers with multifocal, diffuse, or degenerative neurological disease or with pain unrelated to the neurological deficit. We obtained supportive imaging evidence (CT or MRI) on all participants unless contraindicated or complicated by the presence of metal (NP patient 8, Table 1). We required CP patients to have nociceptive sensory impairment within the site of neurologic impairment and pain within this site as their chief complaint; patients selected for the NP group also had lesion-related nociceptive sensory impairment but without pain. One of us (KLC) performed a complete neurological examination on all patients and a screening neurological examination on all HC participants. Each participant received \$350 for completing both the psychophysical and PET imaging components of this investigation.

Psychophysical testing

We obtained bilateral thresholds for heat detection (HD), heat pain threshold (HPT), and heat tolerance (HPTol) on all participants in separate sessions outside the PET scanner several days before PET scanning. Thermal stimulation was performed by a single examiner using the method of limits with a 16mm² digitally controlled contact thermode (TSA)-2001 thermal stimulator, Medoc Advanced Medical Systems, Ramat Yishay, Israel) applied to the skin of the clinically involved and uninvolved sites (usually volar forearm). Baseline thermode temperature was 32°C and the rate of temperature increase was 1°C/s for each determination of at least 5 trials. The area of stimulation was slightly altered for each trial to prevent sensitization.

During scanning, we applied heat to the skin of each volar forearm using a thermal probe (Cygnus/GLC, Inc., Paterson, N.J.) with preset temperatures as previously described [26]. We used the previously obtained threshold information to guide the determination of these thresholds by the method of limits while each participant was in the scanner. In addition, we instructed all participants in the use of a visual analog scale (ruler with sliding marker) to rate the intensity of a series of 5s duration heat stimuli using the following anchors: 0 = no heat sensation, 5 = just painful heat, and 10 = intolerable heat. Participants were instructed to identify HPTol as that heat pain sensation that could not be tolerated if applied for longer than 5s; however, to avoid tissue damage, a limit of 50°C was established for an HPTol stimulus. After receiving instructions on distinguishing sensory intensity from sensory unpleasantness [86], all participants were asked to rate the unpleasantness of the stimulation using the following anchors: 0 = not unpleasant, 10 = the most unpleasant imaginable. We used the left forearm for threshold determinations in the HC group; for the patients, we determined thresholds separately for the clinically affected and unaffected limbs.

PET Procedures

To detect group or individual differences in regional neuronal excitability, it is necessary to have a temporally stable measure of rCBF in the resting (no stimulus) condition so that the change in activation intensity during heat stimulation can be estimated accurately; this is especially true when comparing healthy individuals and patients with variable types of CNS pathology. Because of the problem of baseline drift in fMRI [98, 119], we used PET H₂¹⁵O activation methods to provide long duration (~60s) estimates of baseline regional perfusion (rCBF).

We performed all scans on a Siemens/CTI ECAT EXACT PET scanner operated in 3D data acquisition mode to maximize signal intensity, thus permitting multiple scans of individual subjects with intravenous H₂¹⁵O doses at relatively low levels of radioactivity (10 mCi/scan). We monitored the blood pressure and oxygenation (pulse oximeter) of all participants during scanning. The scanner provides 47 tomographic slices covering an axial field of view of approximately 16 cm. We used a soft restraint and laser beam positioning on facial fiducial marks to help maintain head position; additionally, a computer coregistration algorithm corrected small head motion for each subject before the beginning of analysis [68]. We used a transmission scan to correct attenuation on emission scans. To allow for radioactive decay, at least 10 min elapsed between each scan. Data acquisition began 5s after the estimated arrival of radioactivity in the brain and continued for approximately 60 sec. We analyzed only those voxels with normalized CBF values greater than 60% of the global value (gray matter voxels) using stereotactic anatomical standardization techniques [67, 70, 69]. After normalizing each image set to whole brain counts [40], we created mean radioactivity concentration images estimating regional cerebral blood flow (rCBF) for each experimental condition for each subject. Subtraction images were made for each

subject by subtracting the images acquired during baseline (rest) from those acquired during heat stimulation. A voxel-by-voxel statistical subtraction analysis (Z-score) with adjustment for multiple comparisons was performed as described previously [27, 102] by estimating the smoothness of subtraction images following 3 dimensional Gaussian filtering (FWHM = 9mm) to enhance signal-to-noise ratio and compensate for anatomical variance. Voxels showing a significantly increased CBF compared to the average noise variance computed across all voxels (pooled variance) were identified. The critical level of significance ($Z = 2.0$) was determined by adjusting $p=0.05$ using this information. Only those voxels with normalized CBF values larger than 60% of the global value were analyzed in this study. We used these estimates of rCBF to compute the stimulation-induced percentage change of rCBF from the resting (no stimulus) condition.

The *structures* of interest for this study were selected based on the results of previous PET studies of heat pain performed in this and other facilities [22, 1]. To reduce residual anatomical variance in the stereotactic coordinate system, we first used a standard atlas [104] to identify the stereotactic coordinates of peak activation within each structure of interest within the group of normal subjects; we used these coordinates as a center for the development of *volumes* of interest (VOI) within those structures. We developed standard three-dimensional VOI (Table 2) from the rCBF responses (activation threshold: $Z > 2.5$) of normal subjects to the highest intensity stimulus (HPTol) as described previously [27]. We determined the final coordinate peaks (Table 2) and the size and shape of each VOI separately for each of the structures by methods used and described previously [15, 26, 27]. With the exception of the dorsal and ventral caudate, one or more of the peak activation coordinates of adjacent or nearby structures is separated by at least 5mm, well within the spatial resolution reported in previous studies using this functional imaging technique. We applied these VOI to each hemisphere of each subject at rest and in each stimulus condition within the structures of interest. These standard VOI were applied throughout the study to compare the levels of activation in each stimulus condition for each individual and between groups.

Experimental procedure during scanning—After participants were positioned in the scanner and before scanning began, we again applied 5s contact heat temperatures at the previously determined HD, HPT, and HPTol levels to determine their reliability, making 1-2 °C adjustments as necessary to accommodate any perceptual changes associated with the scanning environment. During scanning, these 3 levels of heat were applied pseudorandomly to the volar surfaces of each forearm (or lower legs of CP patient #1) of the clinically affected and unaffected sides of the body. Heat stimuli were preset at one of the three threshold temperatures and applied repetitively for 5s, moving each contact site between stimuli, throughout the duration of each scan (about 60s). We applied 5s duration contact heat stimuli repetitively to different sites. After each scan, we showed the VAS ruler to each participant and moved the sliding indicator to the number chosen for rating the intensity and unpleasantness of that series of heat stimuli. Inter-scan intervals were approximately 10 minutes. Table 3 shows the stimulation protocol and sequence for the 3 stimulus intensities used during each PET data acquisition session.

Data Analysis

We used SPSS (Chicago, IL, U.S.A.) version 17 for all statistical analysis. For the psychophysical studies, we used univariate ANOVA with Tukey post-hoc comparisons to analyze group differences in the temperatures and VAS numbers chosen for each heat stimulus category (HD, HPT, and HPTol). We used repeated measures ANOVA to examine group and stimulus intensity differences and interactions in the normalized VAS rating differences between the clinically involved and uninvolved body sides. In addition, we used

non-parametric statistics (Kruskal-Wallis) to analyze group differences, by number of participants and number of stimuli, in the lateralization (side difference) of ratings of heat intensity. In the event of a group effect, we used the Mann-Whitney U test to examine group differences between CP and NP patient groups.

We chose non-parametric analytical methods to examine group differences in regional excitability (percentage change from baseline) among VOI because of the small sample size in this study and the individual pathophysiological differences, such as the nature and location of the central lesion, among participants in the patient groups. After examining the frequency distribution of the percentage change from the resting baseline of the rCBF during stimulation at HPT of all VOI in all HC participants, we used the Kruskal-Wallis and median tests to examine group differences in the number of VOI with out of range Z-scores (≥ 2 or < -2 ; $Z = [\text{individual \%change from rest} - \text{HC group mean \%change from rest}] / \text{HC group standard deviation \%change from rest}$). Outliers were identified as values outside 1.5 times the 25th or 75th percentiles as provided in SPSS v 17. We considered VOI with Z scores ≥ 2 as hyperactive at rest or hyper-responsive during stimulation; VOI with Z scores < -2 were considered hypoactive at rest or hypo-responsive during stimulation. We used the Kruskal-Wallis and median tests also to examine group differences in the regional (VOI-wise) distribution of these Z score measurements. In the event of a group effect, we used the Mann-Whitney U test to examine group differences between CP and NP patient groups. For group comparisons, we corrected for the larger number of participants in the HC group by applying the following formula: $(\# \text{ (or sum) of Z scores} / N) \times 100$.

RESULTS

Psychophysics

The average threshold temperatures selected for the stimulus categories *in the noxious range* is not different among groups; however, both the CP and NP patients have average heat detection (HD) thresholds that are slightly higher than the HC group ($F_{2,32} = 7.15$; $p < 0.003$; Table 4). Only 2 patients have HD thresholds below the mean or median of the HC group. In addition, the CP group gave higher average VAS heat intensity ratings for each stimulus category ($F_{2,101} = 133.2$, $p < 0.008$; Table 4). We detected no group rating differences of unpleasantness. Note that these threshold and rating differences do not reflect abnormalities on the side of clinical involvement because, for this pre-scanning analysis in the patient groups, we used data obtained from stimulating the clinically *uninvolved* side.

To examine lateralized (side-to-side) differences in the heat intensity and unpleasantness ratings during scanning, we first normalized the lateralized rating differences for each patient $([\text{VAS clinically normal side} - \text{VAS clinically affected side}] / \text{VAS clinically normal side})$ so that a positive number reflects a decreased rating on the clinically affected side; this normalization is necessary because of individual differences in the numbers chosen by each participant for the VAS rating. For the HC group, we applied the same formula but substituted the right side for “normal” and the left side for “affected”. The average normalized differences in lateralized VAS ratings across all stimulus intensities are positive for both CP and NP groups ($0.182 \pm 0.065\text{se}$; $0.084 \pm 0.066\text{se}$ respectively), but nearly zero (-0.007) for the HC group, consistent with reduced heat intensity perception on the clinically involved side among patients and with a lack of side preference among healthy participants. A repeated measures ANOVA on these average normalized differences reveals a trend of group effect ($p = 0.079$; $F_{2,91} = 2.605$), no effect of stimulus intensity ($p = 0.562$), and no group by stimulus intensity interaction ($p = 0.532$). However, this analysis is sensitive to the *degree* of lateralized perceived difference, which is of less interest in this study than the *distribution* of differences (independent of degree) among the 3 groups. Thus, in a non-parametric analysis, we find a significant group effect on the number of participants

who show a lateralized average normalized difference in the VAS rating for heat intensity (but not for unpleasantness) for 2 or more of the 3 stimulus intensities (Kruskal – Wallis $\chi^2_{df 2} = 7.92$, $p < 0.019$). As shown in Figure 1, the entire NP group and 7 (70%) of the CP group have *lower* intensity ratings of the same stimulus applied to the clinically *affected* side. Only 7 (47%) of the HC group shows a lateralized preference for 2 or more stimulus intensities. We also find a group effect on the number of stimuli for which there is a lateralized difference for intensity ratings at all applied intensities (Kruskal-Wallis $\chi^2_{df 2} = 15.8$, $p < 0.010$) and a similar group effect for perceived unpleasantness (Kruskal-Wallis $\chi^2_{df 2} = 9.16$, $p < 0.010$). Thus, 22 (73%) of the stimuli applied to the CP group and 25 (83%) of the stimuli applied to the NP group receive lower intensity ratings when the same stimulus is applied to the clinically affected side; in contrast, only 23 (51%) of the stimuli applied to the HC group show a lateralized intensity preference.

The results of the psychophysical studies thus confirm the clinical impression that, in comparison with the HC group of males in the same age range, both patient groups have a reduced perception of heat intensity and, by at least one measure, heat unpleasantness on the clinically affected side. In addition, there is an impairment of heat intensity perception (heat detection thresholds) on the clinically *unaffected* side among both NP and CP patients.

Functional imaging

The activation images for the HC group are shown in Figure 2 (see also Table 2). At rest, there is no lateralized (side-to-side) difference in estimated resting rCBF among VOI among healthy subjects ($F_{1,504} = 0.260$, $p = 0.610$), nor is there a significant interaction of side and location of resting activity ($F_{17,504} = 0.945$, $p = 0.521$). Because we use the percentage change from rest as an estimate of excitability during stimulation, and Z-scores of ≥ 2 or ≤ -2 from the HC group mean as evidence of hyper- or hypo-excitability, we examined the distribution of excitability among all VOI in the HC group during stimulation of either side. The distribution of this metric is not normal according to the Kolmogorov-Smirnov test (K-S statistics: 0.062 L stimulation, 0.072 R stimulation; $p < 0.001$) presumably because of 4 outlying frontal lobe activations in one participant. However, the frequency distribution of VOI excitability is unimodal and, by inspection, fits closely a superimposed normal curve as shown in Figure 3 during stimulation at HPT, for example. Therefore, we proceeded with the use of Z scores as estimates of deviation from the mean of VOI excitability within the HC group.

There is a significant group difference among healthy participants (HC), patients without pain (NP), and patients with central pain (CP) in the total percentage of hyperactive ($Z \geq 2$) and hypoactive ($Z \leq -2$) VOIs at rest (Figure 4; Kruskal Wallis test: hyperactive, $\chi^2_{df 2} = 7.53$, $p < 0.023$; hypoactive, $\chi^2_{df 2} = 14.08$, $p < 0.001$). This difference persists after excluding three outlying values. The Mann-Whitney U test shows no difference in these measures between NP and CP groups at rest ($U = 49$, $p = 0.94$ and $U = 40$, $p = 0.45$ for hyper-active and hypo-active VOIs, respectively).

At rest, there is also a significant group difference in the anatomical distribution of hyper- and hypo-active VOIs (Kruskal Wallis test: hyper-active, $\chi^2_{df 2} = 21.16$, $p < 0.001$; hypo-active, $\chi^2_{df 2} = 23.49$, $p < 0.001$). This difference persists after excluding three outlying values. Chi-square tests of each VOI show no right-left (lateralized) effect ($p > 0.05$). Inspection of the data (Figure 5) shows that both NP and CP groups have more hyper- and hypoactive VOI at rest than the HC group; however, the Mann-Whitney U test shows no difference in these measures between NP and CP groups at rest ($U = 572$, $p = 0.36$ and $U = 637$, $p = 0.90$ for hyper-active and hypo-active VOIs, respectively).

During stimulation, there is a group difference in the number of out of range Z scores among subjects (Kruskal Wallis test: hyper-responsive, $\chi^2_{df\ 2} = 14.40$, $p < 0.002$; hypo-responsive, $\chi^2_{df\ 2} = 23.65$, $p < 0.001$); we did not detect an effect of the three levels stimulus intensity (K-W test: hyper-responsive, $\chi^2_{df\ 2} = 1.46$, $p = 0.48$; hypo-responsive, $\chi^2_{df\ 2} = 0.045$, $p = 0.98$). Inspection of the data (Figure 6) again shows that both NP and CP groups have more hyper- and hypo-responsive VOI during stimulation than the HC group; however, the Mann-Whitney U test shows no difference in these measures between NP and CP groups at rest ($U = 438$, $p > 0.86$ and $U = 386$, $p = 0.34$ for hyper-active and hypo-active VOIs, respectively).

During stimulation, and across all stimulus intensity levels, there is also a group difference in the anatomical distribution of both hyper- and hypo-responsive VOI (Figure 7; Kruskal Wallis test, hyper-active, $\chi^2_{df\ 2} = 7.80$, $p < 0.020$; hypo-active, $\chi^2_{df\ 2} = 9.52$, $p < 0.009$). This difference persists, and in fact increases, after excluding two outliers. As noted above, there is no group effect of stimulus intensity. Chi-square tests of each VOI show no right-left (lateralized) effect of stimulation ($p > 0.05$). Inspection of the data shows that both NP and CP groups have more hyper- and hypo-responsive VOI during stimulation than the HC group. Of particular relevance for the purpose of this study, however, a post-hoc Mann-Whitney U test shows a difference between NP and CP groups in the number of hyper-responsive ($U = 452$, $p = 0.02$), but not hypo-responsive ($U = 494$, $p = 0.08$), VOI during stimulation.

The frequency distribution of the differences among hyper-responsive VOI (CP group – NP group) is not uniform (Figure 8; Kolmogorov-Smirnov one-sample test, $Z = 2.17$, p (2-tailed) < 0.001). Inspection of these differences shows that only the intralaminar thalamus (IT), ventral caudate (VC) and the somatosensory-somatomotor (S1M1) cerebral cortex are more frequently hyper-responsive among CP than among NP patients. All other hyper-responsive VOI appear with either less or equal frequency in the CP group. Seven CP patients and 5 NP patients have hyper-responsive VOI within the S1M1 cortex during one or more stimulus trials; 4 CP patients, but no NP patients, have a hyper-responsive VOI in the intralaminar thalamus (IT). There are more hyper-responsive ($N = 11$ vs 5) and fewer hypo-responsive ($N = 1$ vs 5) intralaminar thalamic or S1M1 cortical VOI among CP than among NP patients ($\chi^2_{df\ 1} = 4.54$, $p < 0.033$). The hyper-responsive thalamus or cortex in CP patients is contralateral to the pain in 5 patients, ipsilateral in 2, and bilateral in the remainder.

Figure 9 shows an example of a CP patient (patient # 1, Table 1) with a clinically determined left spinothalamic tract lesion (~T8 level), heat allodynia, and a hyper-responsive intralaminar thalamus. Note that both the left (partially denervated) and right thalamus is hyper-responsive at stimulus levels below and at the heat pain threshold. This patient also has a hyper-responsive left S1M1 cortex during stimulation of either leg but at HPTol levels only. This example demonstrates the remote effects of a single lesion on central nociceptive mechanisms.

DISCUSSION

Psychophysics

Both NP and CP patients had reduced heat intensity sensation on the clinically affected side, a finding in accord with those of other investigators [10, 9, 108, 25, 13, 38]. In addition, both NP and CP patients had a higher HD on the clinically unaffected side compared with the HC group. This finding contrasts with the generalized increased pain sensitivity found during experimental acute or chronic nociceptive pain [57]; moreover, it has not been reported in previous similar investigations possibly because the clinically unaffected side was used as a within-patient comparison. The HD finding suggests that the focal CNS

lesions in both patient groups caused a bilateral impairment of heat sensory function that was clinically detected only contralateral to the lesion. It is possible that undetected CNS lesions caused sensory losses on the unaffected side but this is unlikely because such lesions would have to be present in 80% (16/20) of patients. This result may also reflect the presence of the few ventrolateral thalamic and S1 cortical neurons that are bilaterally responsive to heat stimuli in non-human primates [52, 32]. Clinical observations have long provided evidence for bilateral nociceptive transmission that is normally suppressed when both spinothalamic pathways are intact [74, 11, 73, 72]. Finally, we note that CP patients chose higher VAS ratings for each stimulus category compared to both NP and HC groups but we do not have a neurophysiological hypothesis for this observation. Overall, the psychophysical results reveal a bilateral effect of a CNS lesion that produces a clinically contralateral effect.

Imaging at rest

At rest, NP and CP patients had more VOI that were hyperactive or hypoactive than HC participants. We did not detect a laterality difference in this measurement nor did we find a group difference between NP and CP patients. The anatomical distribution of hyperactive and hypoactive VOI was also different among the three groups but not between NP and CP patients. The group difference in the anatomical distribution of hyperactive and hypoactive VOI cannot be attributed to any particular VOI or group of VOI; it probably reflects both the wide distribution and the larger number of out of range Z scores among VOI within the patient groups. Thus, the results of the study during the resting condition do not suggest a neurophysiological basis for the resting pain experienced by CP patients. However, the large number and wide distribution of VOI with abnormal activity among NP and CP patients shows that the CNS lesion causing the focal sensory loss has divergent and widely distributed effects.

Imaging during stimulation

During stimulation, NP and CP patients had more hyper-responsive and hypo-responsive VOI than HC participants and there was no group effect of stimulus intensity or laterality. The group difference in the anatomical distribution of these excitability changes again reflects primarily the wide distribution and much larger number of hyper- and hypo-responsive VOI within the patient groups. However, we detected a difference in the anatomical distribution of hyper-responsive, but not hypo-responsive, VOI between NP and CP patients and these differences were not uniformly distributed. As shown in Figures 7 and 8, several structures had fewer hyper-responsive VOI in CP than in NP patients; those with the greatest differences relative to both CP and HC groups include the putamen and the anterior insular, mid-insular, inferior prefrontal (B47), lateral premotor, and secondary somatosensory (S2) cortices. It is possible that the relatively reduced number of these hyper-responsive VOI contributes to the pain of our CP patients because they could participate in endogenous analgesic mechanisms [90, 56, 63, 5, 6, 48]. If this hypothesis is correct, however, we would expect to find a relatively increased number of hypo-responsive VOI within these structures among CP patients and thus a significant difference between NP and CP patients in the distribution of hypo-responsive VOI. However, only hyper-responsive VOI were distributed differently between the NP and CP groups. It is therefore unlikely that a relatively reduced hyper-responsiveness of some structures contributes to the pain of CP patients. Rather, the pain of our CP patients is more likely attributable to the uniquely increased number of hyper-responsive VOI within the intralaminar thalamus (IT) and primary sensory-motor cortex (S1/M1) as shown in Figures 7 and 8. The ventral caudate (VC) also has slightly more hyper-responsive VOI among CP patients, but the total number of VOI is small compared to the other two structures. All CP patients but one (90%) showed

hyper-responsiveness in either the intralaminar thalamus, S1/M1 cortex, or in both structures; in contrast, 5 NP patients (50%) had hyper-responsive VOI in these structures.

Physiological significance of IL thalamic and S1M1 hyper-responsiveness in CP patients

Our findings may not apply to CP patients generally because our sample size is small and the pathophysiology of CP is not likely to be identical or even similar across a larger sample of patients. Nonetheless, the intralaminar thalamus and primary sensory-motor cortex are likely candidates for participation in mediating the pain of CP. The primate intralaminar thalamus receives direct input from the spinothalamic tract [65, 7, 50, 99, 2, 36], shows cellular responses to noxious stimuli [21, 16, 58, 51, 91], and is among the thalamic structures regularly activated in functional imaging studies of pain in humans [22, 81, 85, 1]. Furthermore, thalamo-cortical intralaminar thalamic cells send axons directly to the anterior cingulate cortex [111, 110], which also shows differential cellular and evoked potential responses to noxious stimuli [62, 96, 47, 97] and is among the structures most commonly activated in human pain imaging studies [22, 81, 1]. Focal lesions within the anterior cingulate cortex have been used to alleviate the affective component of chronic pain [39, 33, 117]. Based on clinical and neurophysiological evidence, the intralaminar thalamic-anterior cingulate pathway has long been associated with mediating the affective component of pain [39, 112, 109]. Similarly, the sensory-motor cortex receives nociceptive input via the ventrolateral thalamic nuclei, shows differential or selective cellular and evoked potential responses to noxious stimuli in human and non-human primates [52, 84, 53, 83, 77, 116], and is among the structures activated in pain imaging studies of humans [17, 81, 1]. Lesions within the territory of the primary sensory-motor cortex may attenuate pain in restricted body areas according to a few reports [92, 64]. Notably, electrical stimulation of the motor cortex has been reported to be effective in the treatment of chronic pain, including intractable CP [106, 79, 76, 20, 89, 63]. Overall, the weight of clinical and electrophysiological evidence supports the hypothesis that the sensory-motor cortex participates in mediating the sensory-discriminative, but not affective, components of pain [82, 94, 83]. Thus, a unique nociceptive excitability increase in the intralaminar thalamus and somatosensory cortex may contribute to the pain in some patients with central pain syndrome.

Widespread excitability changes in NP and CP patients

Our results provide additional evidence for the anatomically distributed effects of focal CNS lesions, a phenomenon clearly recognized in the 19th and early 20th centuries [71] and further documented in contemporary brain imaging studies [78, 103, 3]. Focal lesions are often followed by an extensive anatomical and functional reorganization of sensory and motor pathways [31, 114, 115, 75, 30]. The changes following focal injury include widespread altered excitability [66] and changes in the amount and activity of several neurotransmitters and neurotrophic factors [100, 41, 66, 87], gamma-amino-butyric acid (GABA) being among the most frequently implicated in the pathophysiology of post-stroke or post-traumatic central pain [88, 107, 18, 24, 43]. The recent study of Willoch and colleagues [118] reveals further the widespread effect of focal subcortical lesions on cerebral opioid receptor binding and its presumed effect on endogenous analgesia mechanisms [14, 120, 23]. Given the results presented here, some aspects of a thalamic disinhibition hypothesis deserve consideration also [44, 37, 34].

Conclusion

NP and CP patients have bilaterally reduced heat detection, unilaterally reduced heat sensory ratings, and more brain areas with altered resting activity and heat-evoked excitability than an aged-matched group of healthy individuals. Compared to HC participants and NP patients, CP patients have more hyper-responsive areas in the intralaminar thalamus and

sensory-motor cortex. Our results thus confirm the widely distributed effects of focal CNS lesions and suggest that a unique pattern of nociceptive excitability change may underlie the pain in some patients with central pain syndrome.

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Figure 1.

Number of healthy control participants (HC; N = 15), central pain patients (CP; N = 10), and patients with sensory loss but no pain (NP; N = 10), who have a lower average normalized VAS rating of an identical heat stimulus on the clinically affected (patients) or left (HC) side for 3 (black bars), 2 (gray bars), or 1-0 (white bars) applied stimulus intensity levels.

Figure 2.

Statistical parametric maps (Z score color code in center) of the regional cerebral blood flow (rCBF) responses from baseline ($H_2^{15}O$ PET) to repetitive 5s contact heat stimulation of the left or right volar forearm in a group of healthy participants, ages 42-54. Transverse brain images shown at selected levels above the anterior-posterior commissure plane; right hemisphere is to the reader's left. Stimulus intensities were psychophysically determined for each individual. HD: heat detection. HPT: heat pain threshold. HPTol: heat pain tolerance.

Figure 3.
Frequency histograms of the percentage change from baseline rCBF among HC participants during heat stimulation of either side at HPT. A normal distribution curve is superimposed on the histogram.

Figure 4.

Group percentages of total number of hyperactive ($Z \geq 2$) and hypoactive ($Z < -2$) VOI among HC (white bars; $N = 15$), NP (gray bars; $N = 10$), and CP (black bars; $N = 10$) groups at rest (baseline rCBF).

Figure 5. Anatomical distribution of group percentages of the total number of hyperactive and hypoactive VOI among HC, NP, and CP groups. See Table 2 for abbreviations.

Figure 6.

Group percentages of the total number of hyper-responsive and hypo-responsive VOI among HC, NP, and CP groups during heat stimulation at HD, HPT, and HPTol perceived intensity levels.

Figure 7.
Anatomical distribution of group percentages of the total number of hyper-responsive and hypo-responsive VOI among HC, NP, and CP groups at all levels of heat stimulation.

Figure 8.

Anatomical distribution of the differences between CP and NP patients (CP-NP) in the group percentage of the total number of VOI that are hyper-responsive during heat stimulation at all levels of perceived intensity.

Figure 9.

Statistical parametric maps (Z score color code at right) of the regional cerebral blood flow (rCBF) responses from baseline (H_2^{15}O PET) to repetitive 5s contact heat stimulation at heat detection (HD) and heat pain threshold levels (HPT). Imaging orientation conventions as in Figure 2. Top row of images are from CP patient # 1, who had heat allodynia of the right body below the T8 dermatome due to a lesion clinically identified as a stroke involving the right spinothalamic tract. Bottom row of images show the average responses at the same levels from the (normal) HC group. Arrows indicate the excessive responses primarily, but not exclusively, in the thalamus ipsilateral to the spinal cord lesion.

Table 1

A. Demographic characteristics of CP patients. B. Demographic characteristics of NP patients. Summary of the demographic characteristics of the 15 HC participants is shown below.

A						
CENTRAL PAIN (CP)						
ID	GENDER	AGE	ETHNICITY	CLINICAL EVALUATION	PAIN ONSET/DURATION	PAIN Rx
						RATING OF ONGOING PAIN
1	M	51	C	Lt. spinothalamic post-op stroke at T8; Rt. heat & tactile allodynia, temp and pinprick loss	<1 month/2 years	NT (-)
2	M	60	C	Lt. thalamic stroke, Rt. hemibody electric dysesthesias, deep pain & temp loss, tactile allodynia	immediate/3 years	CB(-)
3	M	66	C	Rt. thalamic stroke, Lt. hemibody painful paresthesias, heat & cold allodynia, pinprick hyperalgesia	immediate/5 years	NT (+/-)
4	M	54	C	Lt. C6-T2 syrinx, Lt. arm & hand pain, absent temp, reduced pinprick & tactile	unknown/2 years	OP (+/-); GP(+/-)
5	M	52	C	Rt. hemisphere stroke, Lt. hemiparesis, arm and hand pain; tactile allodynia	immediately post-op/2years	OP (+/-)
6	M	56	C	Rt. thalamic stroke, Lt. hemibody pain; pin, temp, sensory loss	immediate/7 years	none
7	M	52	C	Lt. temporoparietal stroke, Rt. hemibody pain, tactile & pinprick loss; valproic acid for seizures	7months/5 years	NT (-)
8	M	51	C	Lt. thalamic stroke; pain Rt. trunk, arm and hand (elevated laser pain threshold); cold allodynia	< 1 week/1 year	NT (+/-)
9	M	48	AA	Rt. hemisphere stroke, Lt. hemibody loss tactile & pinprick; pressure allodynia	<1month/1 year	NT (-)
10	F	48	As	Rt. thalamic hemorrhage, Lt. hemibody global hypalgesia;arm & foot pain	4months/9 months	GP (-)

B					
CENTRAL LESION, NO PAIN (NP)					
ID	GENDER	AGE	ETHNICITY	CLINICAL EVALUATION	LESION ONSET/DURATION
1	M	55	C	Lt. thalamic stroke, Rt. hemibody loss temp & pinprick > touch	<1 month/2 years
2	M	68	AA	Lt. hemisphere stroke, Rt. hemibody decreased pinprick & cold	immediate/3 years
3	M	47	C	Lt. parieto-temporal stroke; decreased pinprick Rt. arm & leg	immediate/5 years
4	M	40	C	Rt. hemisphere perinatal stroke; valproic acid for seizures; pin, temp, & tactile sensory loss	unknown/2 years
5	M	50	C	Lt. thalamic stroke, Rt. hemibody decreased pinprick > temp	immediately post-op/2years

6	M	58	C	Lt. thalamic stroke, Rt. painless paresthesias arm & leg, reduced pinprick & tactile sensation	immediate/7 years
7	M	50	C	Lt. hemisphere trauma, Rt. hemibody decreased pinprick, temp, tactile sensation	7months/5 years
8	M	50	C	Rt. hemisphere shrapnel wound; Lt. temp, pin, tactile hemibody sensory loss; phenytoin for seizures	< 1 week/1 year
9	M	47	C	Lt. cervical dorsal cord lesion due to trauma; Lt. Babinski reflex; areflexic, flaccid Lt.arm; global sensory loss	<1month/1 year
10	M	50	C	Lt. int capsule/thalamic stroke. Rt. hemibody decreased temp >touch	4months/9 months

C = Caucasian, AA = African-American, As = Asian

(-) = no effect on pain, (+) = reduces pain, , GP= gabapentin, OP= opioid, NT= nortriptyline, CB = carbamazepine

HEALTHY CONTROL (HC) GROUP (summary)

mean age: 49, median age: 49, age range: 42-64

ethnicity: 8 C, 6 AA, 1 As

Table 2

Identification, abbreviation, and Talairach coordinates [100] of the peak activation coordinates of volumes of interest (VOI) based on the activation within structures of interest in the group of HC participants.

STRUCTURE (ABBREVIATION)	VOI COORDINATE PEAKS (X,Y,Z)
MEDIAL THALAMUS (MT)	(6,-15, 9/11)
INTRALAMINAR THALAMUS (IT)	(8, -10, 9)
VENTROLATERAL THALAMUS (VT)	(17, -13, 16)
PUTAMEN (P)	(24, 5, 7)
DORSAL CAUDATE (DC)	(17, 14, 11)
VENTRAL CAUDATE (VC)	(15, 14, 4)
ANTERIOR INSULA (AI)	(39, 12, 9)
MID-INSULA (MI)	(44, 3, 9)
INFERIOR FRONTAL CORTEX (B45)	(46, 23, 7)
INFERIOR FRONTAL CORTEX (B47)	(37, 41, -4)
MEDIAL FRONTAL CORTEX (B10)	(26, 46, -4)
ORBITOFRONTAL CORTEX (B11)	(24, 44,-18/20)
DORSAL PREMOTOR CORTEX (B6)	(12, -1, 63)
LATERAL PREMOTOR CORTEX (LPM)	(53, 3, 11)
SECONDARY SOMATOSENSORY CORTEX (S2)	(44, -15, 16)
SENSORIMOTOR CORTEX (M1/S1)	(26, -22, 58)
SENSORIMOTOR CORTEX (S1/M1)	(33, -24, 65)
PREGENUAL CINGULATE CORTEX (PGC)	(21, 35, 4)

Table 3

Protocol sheet for the acquisition of PET scanning data for each participant.

CENTRAL PAIN PROTOCOL: 3D PET									
Thermal Stimulation		Detection	Threshold		VAS scores				
		Temp1	Temp2			Temp3			
	Side	Stimulation	Time	Counts	Pain	Unpleasantness	COMMENTS		
SCAN1	RIGHT	Temp1							
SCAN2	RIGHT	Temp3							
SCAN3	RIGHT	Temp2							
SCAN4	LEFT	Temp1							
SCAN5	LEFT	Temp3							
SCAN6	LEFT	Temp2							
SCAN7	BASELINE	None							
SCAN8	LEFT	Temp3							
SCAN9	LEFT	Temp1							
SCAN10	LEFT	Temp2							
SCAN11	RIGHT	Temp3							
SCAN12	RIGHT	Temp1							
SCAN13	RIGHT	Temp2							
SCAN14	BASELINE	NONE							
SCAN15	RIGHT	Temp2							
SCAN16	RIGHT	Temp3							
SCAN17	RIGHT	Temp1							
SCAN18	LEFT	Temp2							
SCAN19	LEFT	Temp3							
SCAN20	LEFT	Temp1							
SCAN21	BASELINE	NONE							

Table 4

Average (s.e.m.) temperatures and VAS ratings chosen by HC, NP, and CP participants for perceived heat detection (HD), heat pain threshold (HPT), and heat pain tolerance (HPTol) during stimulation of the right (HC group) or clinically uninvolved volar forearm (patients) immediately before scanning.

		mean (s.e.m.)		
		HC	NP	CP
HD	°C	38.6 (0.37)	41.2 (0.71) *	40.6 (0.72) *
	VAS	2.35 (0.24)	1.89 (0.21)	2.98 (0.50) **
HPT	°C	46.4 (0.97)	46.9 (0.66)	47.2 (0.45)
	VAS	4.64 (0.35)	4.70 (0.47)	5.43 (0.41) **
HPTol	°C	49.4 (0.91)	49.2 (0.55)	50.0 (0.36)
	VAS	7.82 (0.23)	7.55 (0.37)	8.46 (0.38) **

* higher than HC group (post hoc comparisons: $p < 0.031$ for NP and $p < 0.004$ for CP groups)

** greater than HC and NP groups (post hoc comparisons: $p < 0.003$ for NP and < 0.015 for HC groups)