Assessing the risk of central post-stroke pain of thalamic origin by lesion mapping

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Central post-stroke pain of thalamic origin is an extremely distressing and often refractory disorder. There are no well-established predictors for pain development after thalamic stroke, and the role of different thalamic nuclei is unclear. Here, we used structural magnetic resonance imaging to identify the thalamic nuclei, specifically implicated in the generation of central post-stroke pain of thalamic origin. Lesions of 10 patients with central post-stroke pain of thalamic origin and 10 control patients with thalamic strokes without pain were identified as volumes of interest on magnetic resonance imaging data. Non-linear deformations were estimated to match each image with a high-resolution template and were applied to each volume of interest. By using a digital atlas of the thalamus, we elucidated the involvement of different nuclei with respect to each lesion. Patient and control volumes of interest were summed separately to identify unique areas of involvement. Voxelwise odds ratio maps were calculated to localize the anatomical site where lesions put patients at risk of developing central post-stroke pain of thalamic origin. In the patients with pain, mainly lateral and posterior thalamic nuclei were affected, whereas a more anterior–medial lesion pattern was evident in the controls. The lesions of 9 of 10 pain patients overlapped at the border of the ventral posterior nucleus and the pulvinar, coinciding with the ventrocaudalis portae nucleus. The lesions of this area showed an odds ratio of 81 in favour of developing thalamic pain. The high odds ratio at the ventral posterior nucleus-pulvinar border zone indicates that this area is crucial in the pathogenesis of thalamic pain and demonstrates the feasibility of identifying patients at risk of developing central post-stroke pain of thalamic origin early after thalamic insults. This provides a basis for pre-emptive treatment studies.

Keywords: thalamic nuclei; stroke; pain; magnetic resonance imaging; brain mapping
Introduction

Central post-stroke pain of thalamic origin was first described by Dejerine and Roussy (1906) and is characterized by neuropathic pain emerging from thalamic lesions such as infarctions or bleeds. A prevalence of ~7% of stroke patients has been reported in isolated thalamic strokes (Bogousslavsky et al., 1988; Andersen et al., 1995), although epidemiological data are scarce. Symptoms are typically characterized by severe, burning hemibody pain contralateral to the thalamic lesion, and central post-stroke pain of thalamic origin is considered to be one of the most distressing pain syndromes (Klit et al., 2009). Pain is often accompanied by sensory abnormalities such as negative symptoms (e.g. thermosensory deficits) and positive symptoms (e.g. dysaesthesias). A different pattern of sensory signs and symptoms has been suggested previously in central post-stroke pain of thalamic origin when compared with central post-stroke pain of non-thalamic origin, e.g. with spinal, brainstem or cortical lesions (Riddoch, 1938a; b; Bowsher et al., 1998), although they can be indistinguishable in individual patients (Riddoch, 1938b; Kalita et al., 2011). Regarding supratentorial causes of central post-stroke pain, it has been suggested that central post-stroke pain of operculo-insular origin is associated with dissociated thermoalgesic sensory loss due to preserved lemniscal function, whereas central post-stroke pain of thalamic origin is usually characterized by non-dissociated symptoms (Garcia-Larrea et al., 2010). It has also been reported that patients with central post-stroke pain of supratentorial origin including thalamic origin have greater deficits in sharpness and cold sensation, whereas patients with central post-stroke pain of infratentorial origin have greater deficits for warmth and hot pain (Bowsher et al., 1998). For clinicians, central post-stroke pain including central post-stroke pain of thalamic origin is a major challenge and is often refractory to treatment (Henry et al., 2008). In many cases, the pain develops with a delay of weeks to months after the CNS lesion (Nasreddine and Saver, 1997). This interval without pain after the lesioning event theoretically opens the door for pre-emptive pharmacological strategies. Predictors would allow the early identification of patients at risk of developing central post-stroke pain of thalamic origin post-infarct. Such patient classification would enable pre-emption treatment or at least provide criteria to group patients in drug studies. Patient age, gender and the laterality of thalamic lesions were all found to be inconsistent predictors in the past (Klit et al., 2009). Studies of pre-emptive therapies have been complicated by the need for accurate predictors and insufficient statistical power. For example, Lampl et al. (2002) studied the effect of amitriptyline as a preventative agent in patients suffering from a thalamic lesion in the ventral posterior complex. However, only 7 of 39 patients studied ever won on to develop central post-stroke pain of thalamic origin (Lampl et al., 2002).

The exact pathophysiological mechanisms leading to central post-stroke pain of thalamic origin are unclear. Most concepts explaining central post-stroke pain of thalamic origin approximate the mechanism proposed by Head and Holmes (1911) and focus on a lesion of lateral nuclei resulting in disinhibition of medial thalamic nuclei. It is not entirely clear which thalamic nuclei are critically involved in the generation of central post-stroke pain of thalamic origin. Previous studies aiming at identifying the critical lesion location with modern brain mapping techniques included very low numbers of patients and used manual or linear atlas-to-MRI registration techniques (Montes et al., 2005; Kim et al., 2007), which have been shown to be inferior compared with non-linear techniques (Chakravarty et al., 2009b). In addition, these previous studies did not include control subjects (Montes et al., 2005; Kim et al., 2007).

In this study, we aimed to determine the mutual lesion site in patients with central post-stroke pain of thalamic origin in standard stereotactic space using structural MRI data. The location of the lesioned thalamic nuclei was determined using a high-resolution multi-structure digital 3D atlas of subcortical anatomy previously created from serial histological data (Chakravarty et al., 2006). We also calculated voxelwise odds ratio maps to quantify the risk of developing central post-stroke pain of thalamic origin with lesions of specific areas of the thalamus.

Materials and methods

Patient recruitment

Ten consecutive patients (seven males and three females) with central post-stroke pain of thalamic origin and 10 control patients (randomly chosen with matching for gender and lesion side) with thalamic infarct but without central post-stroke pain of thalamic origin were recruited from the Department of Neurology and the affiliated Interdisciplinary Pain Centre at the Technische Universität München, Germany (Supplementary Tables 1 and 2). All patients with central post-stroke pain of thalamic origin fulfilled the diagnostic criteria for definite neuropathic pain (Trende et al., 2008) and more specifically definite central post-stroke pain as recently proposed (Klit et al., 2009). Patients and controls had no other chronic pain condition. There was no significant age difference between the groups (Mann–Whitney U test; P = 0.27; average age of the thalamic pain group: 65.5 years; average age of the control group: 60.6 years). As an inclusion criterion, the control patients (without central post-stroke pain) had to have had a follow-up of at least 2 years before study recruitment to exclude the development of pain after a longer latent period. The range of the post-stroke interval in the control patients was 25–62 months. For the patients with central post-stroke pain of thalamic origin, the post-stroke interval at the time of the study varied between 11 months and 16 years. The study was approved by the ethics committee of the Technische Universität München, and written informed consent was obtained from the participants. The study was conducted in accordance with the Declaration of Helsinki.

Magnetic resonance imaging and data analysis

Volumetric structural MRI data were acquired on a Siemens Symphony 1.5 T Scanner with an 8-channel head coil. High-resolution whole-brain T1-weighted MPRAGE sequences (160 slices; slice thickness: 1 mm; voxel size: 1 x 1 x 1 mm3; flip angle: 15°; field of view: 256 x 256 mm; repetition time: 1520 ms; echo time: 3.93 ms; inversion time: 800 ms) were acquired in all patients and controls to determine the lesion site and extent. Conventional whole-brain axial T2 spin-echo and FLAIR images additionally helped to confirm the lesion extent. The
lesions were delineated manually as volumes of interest on the original T1-weighted MRI of all subjects using the MRicro software version 1.4 (http://www.sph.sc.edu/comd/rorden/mricro.html; Rorden et al., 2007). As thalamic pain is a strictly lateralized syndrome, the volume of interest data and MRI data of the patients with left-sided thalamic lesions were flipped about the mid-sagittal plane, such that the affected hemisphere was always the right hemisphere. This enabled a voxelwise analysis of the whole patient and control group. The T1-weighted MRIs were transformed to match a high-contrast and -resolution template in standard stereotaxic space (Montreal Neurological Institute space). The template used was the Colin27 MRI template derived from the voxel-by-voxel averaging of 27 MRI volumes from the same individual (Holmes et al., 1998). MRI data were matched to this template using the ANIMAL algorithm (Collins et al., 1995; Collins and Evans, 1997), which estimates a non-linear transformation by defining a set of local translations on equally spaced nodes through the optimization of the correlation coefficient in a local neighbourhood defined around each node. The lesions were masked out of the non-linear registration process. To accurately match subcortical structures, the optimized atlas-to-patient warping method validated by Chakravarty et al. (2008) was used. Each transformation was applied to each of the lesion volumes of interest, so that anatomical locations could be compared in the same anatomical reference space. In addition, a subcortical atlas derived from a set of serial histological data (Chakravarty et al., 2006) was used to verify the location of the findings. This atlas was originally derived using manually segmented histological data where thalamic definitions are available with respect to both the Hirai and Jones (1989) and Schaltenbrand and Wahren (1977) definitions of the thalamic subnuclei. In addition, these definitions were warped to fit the Colin27 MRI template. Readers are referred to Chakravarty et al. (2006) for the specific definitions of how thalamic subnuclei were defined in the atlas.

Since all volumes of interest were transformed to the reference space defined by the Colin27 magnetic resonance template, anatomical localization of each lesion was determined with respect to the different thalamic nuclei using a two-step automated approach. The volume defined by the warped region of interest and the label defining each thalamic subnucleus (using the Hirai and Jones (1989) nomenclature) was recorded. This allowed us to compare the locations and volumes of these lesions between patient and control groups (Fig. 5; Supplementary Tables 1 and 2). Examples of representative lesions from a patient and a control, which were normalized to the atlas, are available in Supplementary Fig. 1.

The transformed volumes of interest were summed to plot the critical lesion site in thalamic pain. The same was done for the control group separately (Fig. 1).

**Figure 1** (A) Cumulative (summed) lesion map of the patients with thalamic pain (n = 10) in standard stereotaxic space (MNI space). (B) Cumulative lesion map of the control patients (n = 10) in standard stereotaxic space (MNI space). The lesion maps are overlaid on a high-resolution T1 MRI (Colin27 MRI template) in sagittal and coronal planes (Holmes et al., 1998). The colour bars on the right indicate the colour coding of the lesion summation. Please note the different scaling of the images in (A) compared with (B) as indicated by each colour bar.
In addition, voxelwise odds ratio maps (Figs 2 and 3) were calculated for the group. If $N_p$ is the number of patients with central post-stroke pain of thalamic origin, $N_c$ is the number of controls, $V_p$ is the number of patients with a lesion at a specific voxel, and $V_c$ is the number of controls with a lesion at a specific voxel, then the odds ratio at each voxel can be calculated using the following formula:

$$OR = \frac{V_p(N_c - V_c)}{(N_p - V_p)V_c}$$

These maps reflect the risk of developing central post-stroke pain of thalamic origin with a lesion at a specific voxel within the thalamus. To prevent divisions by zero during the calculation of the voxelwise odds ratio maps, voxels with lesions in the patient group and no lesions in the control subjects, were set to a value of 1 in the control group. We chose this conservative substitution to avoid overestimation of the odds ratio values and to avoid division by zero errors.

Finally, we calculated the difference between the summed lesion maps of the pain patients minus the controls (i.e. subtraction maps; Fig. 4) to confirm the results of the odds ratio analysis with a more conventional approach.

**Results**

Five patients with central post-stroke pain of thalamic origin had right-sided lesions and five had left-sided lesions. The same was true for the control patients. The pain syndrome started with the lesioning event in three of the patients. In the seven remaining patients, the pain developed over a period of 15 days to 36 months. Clinical characteristics and the individually lesioned nuclei of the patients and controls are listed in Supplementary Tables 1 and 2, respectively. The ventral posterior nucleus,
pulvinar, centre median and medial geniculate nuclei were most commonly affected in the patients with pain. All these nuclei were lesioned in 9 of 10 patients with central post-stroke pain of thalamic origin (Supplementary Table 1). The largest lesion volume was found in the pulvinar, with a median lesion volume of 569.5 mm³ (interquartile range 519 mm³) in the 10 patients with pain. Figure 5 shows the mean volume occupied in each thalamic subnucleus in both patients and controls. The lesions of the pain-free control subjects most commonly affected the ventral posterior nucleus in 8 of 10 cases, and most of those patients had some sort of somatosensory symptoms other than pain, as shown in Supplementary Table 2.

The lesions of 9 of the 10 patients with central post-stroke pain of thalamic origin overlapped at the border of the pulvinar to the ventral posterior nucleus (Fig. 1; size of the maximal lesion overlap 3 mm³). The position of the maximal lesion overlap was verified using the Schaltenbrand and Wahren (1977) atlas labels defined in the digital atlas used (Chakravarty et al., 2006) and were found to coincide with the ventrocaudalis portae nucleus.

The lesion of only one of the patients with central post-stroke pain of thalamic origin (Patient 10) did not extend to this area of mutual involvement. However, this patient’s lesion was just adjacent to this area.

Figure 1 and Supplementary Tables 1 and 2 clearly indicate that the pattern of affected nuclei differs between patients with and without pain. The control patients tended to have more medial lesions, the patients with central post-stroke pain of thalamic origin had rather lateral and posterior thalamic lesions. Moreover, the total thalamic lesion volume of the patients with pain was clearly larger than in the patients without pain (median volume 953.5 mm³ versus 205.5 mm³; significantly different between groups; Mann–Whitney U test; \( P < 0.05 \) two-tailed). However, there was also one patient with a relatively small thalamic lesion having a clear-cut thalamic pain syndrome (Patient 4).

With the odds ratio approach, we identified voxels with an odds ratio of up to 81 in favour of having thalamic pain (Fig. 2). These voxels where again located at the border of the pulvinar to the ventral posterior nucleus (\( x/y/z \) coordinates of the maximal odds ratio values: \(-14/\pm23/1 \) and \(-14/\pm23/0 \)). These coordinates were also within the ventrocaudalis portae nucleus as defined by the Schaltenbrand and Wahren (1977) atlas labels (Fig. 3). In some patients, the lesion extended into the extrathalamic capsule. In this territory, we found, using the odds ratio paradigm, a region immediately adjacent to the thalamus with a maximum odds ratio value of 5.2.
The subtraction analysis of the lesion overlap in the patients with central post-stroke pain of thalamic origin minus the overlap in the controls yielded very similar results (Fig 4) as the odds ratio approach within the thalamus. Here, the maximal overlap was found at the same coordinates \( (x/y/z) \) coordinates \((-14/-23/1 \) and \(-14/-23/0) \) as for the odds ratio analysis. None of the control patients had lesions at the two noted coordinates. The maximal voxel value of the subtraction analysis was 9.

**Discussion**

This is, to the best of our knowledge, the first study applying odds ratio values on a voxelwise basis using structural MRI data. Odds ratio is a typical measure used in clinical studies such as case-control studies and its application to neuroimaging data proved useful in this study, and the results were confirmed by the conventional subtraction analysis. The very high spatially localized odds ratios observed suggest that stereotaxically normalized imaging data are suitable to predict whether a patient with thalamic stroke will develop central post-stroke pain of thalamic origin depending on the lesion location. The results may pave the way for a larger multi-centre study to investigate this important clinical question in a prospective way, applying the results of the current study (an image file displaying the area with peak odds ratio values as a region of interest will be available at Brain online for download and use in future studies). If a prospective trial confirms that it is indeed possible to identify patients with acute thalamic...
strokes at risk of developing central post-stroke pain of thalamic origin, this would open the door to pre-emptive strategies for thalamic pain. As this pain condition is often extremely refractory to medical treatment (Henry et al., 2008), primary prevention/pre-emptive strategies seem to be the most promising approach to move forward in therapeutic terms, and for this purpose, reliable measures identifying patients at risk are crucial. The next step would then be to test the usefulness of drugs such as antidepressants, anticonvulsants or N-methyl-D-aspartate receptor antagonists in patients with acute thalamic lesions at the critical (‘eloquent’) lesion site before patients develop the clinical pain syndrome. The feasibility of such an approach is underlined by the fact that 7 of 10 patients with pain included in this study, developed the pain within weeks to months after the lesioning event, whereas only three patients suffered from pain instantaneously after the stroke. In most patients, hence, there is a sufficient time window to initiate pre-emptive treatment.

Our results are also of interest in terms of neuroanatomy. We applied a classical lesion mapping approach to determine the site of mutual involvement in patients suffering from central post-stroke pain of thalamic origin. The results indicate that the ventral posterior nucleus/pulvinar border zone is crucial for the development of pain. We verified the location of the maximal odds ratio values with a Schaltenbrand and Wahren (1977) version of the digital atlas indicating that the lesion coincides with the ventrocaudalis portae nucleus. This finding is in line with previous observations reporting that microstimulation of the human ventrocaudalis portae nucleus can produce painful sensations (Lenz et al., 1993). Indeed, stimulation of this area was more likely to produce pain than stimulation of the core of the nucleus ventrocaudalis, and the authors concluded that the posterior-inferior region of the thalamus, including the ventrocaudalis portae nucleus, is functionally distinct from the cutaneous core of ventrocaudalis. The posterior-inferior region appears to contain neural elements involved in pathways signalling pain and temperature (Lenz et al., 1993). Taken together, our data supports the view that central post-stroke pain can be produced by damage to specific neural elements within the thalamus and that lesions of the ventrocaudalis portae nucleus are key in this respect. We strongly believe and our data with high odds ratio values suggest that the exact lesion location rather than the lesion size matters. This view is well in line with previous literature indicating that central post-stroke pain of thalamic origin can follow both small and large lesions of the thalamus and that the lesion volume does not differ between patients with somatosensory deficits with and without central post-stroke pain of thalamic origin (Canavero and Bonicalzi, 2007). Central post-stroke pain seems to be rare in cases with

**Figure 5** Mean group lesion volumes for specific thalamic nuclei in patients with central post-stroke pain of thalamic origin (black) and controls (white) in standard stereotaxic space. The error bars indicate the standard error of the mean. MGN = medial geniculate; LGN = lateral geniculate; VA = ventral anterior; VL = ventral lateral; VP = ventral posterior.
large thalamic lesions (Kameyama, 1976, 1977), again arguing for the importance of location rather than size of the lesion.

It has been suggested previously that the posterior part of the ventral medial nucleus instead of the ventral posterior or ventrocaudalis nucleus is the key region for the development of central post-stroke pain of thalamic origin (Craig, 2003). The VMpo has been suggested to be the relay field of thermosensory and nociceptive lamina I fibres projecting to the dorsal posterior insular cortex (Craig, 2002). According to Craig (2007), the VMpo has been suggested to be the relay field of thermosensory and nociceptive lamina I fibres projecting to the dorsal posterior insular cortex (Craig, 2002). According to Craig (2007), the VMpo-dorsal posterior insular pathway may inhibit a limbic network consisting of the medial thalamus, anterior cingulate cortex and peri-aqueductal grey matter. Central post-stroke pain of thalamic origin could then be seen as a disinhibition disorder of thermoregulatory integration (Craig, 2007). The VMpo has been suggested to be located adjacent to the basal part of the ventral medial nucleus (Craig et al., 1994; Blomqvist et al., 2000), which is at the ventral posterior/pulvinar border zone. Unfortunately, the VMpo is not part of standard thalamic atlases, and therefore, we have no dedicated atlas-based data on whether the lesion volumes affect this region. Altogether, no firm conclusions can be drawn regarding a potential role of this nucleus from our data.

In a previous case report on a patient with central post-stroke pain of thalamic origin, a manual atlas co-registration was used for MRI-based identification of lesioned nuclei. The authors reported that the thalamic lesion did involve the anterior two-thirds of the ventral posterior lateral nucleus and the ventral posterior medial and inferior nuclei, whereas it did not cover the ventral medial nucleus (the authors did not specifically report on involvement of the ventrocaudalis portae nucleus) (Montes et al., 2005). From visual inspection of the published MRI (Montes et al., 2005), it seems that the lesion location of this patient overlaps with the area where we found the highest odds ratio values, being located at the border of the ventral posterior nucleus to the pulvinar. A more recent case series investigating three patients with central post-stroke pain of thalamic origin found that lesions involved the ventrocaudalis in all three patients, while lesions extended into the ventrocaudalis portae nucleus in two of the cases. Lesions were reportedly not affecting the VMpo (Kim et al., 2007). In all three patients, the lesion was located at the border of the ventral posterior nucleus to the pulvinar, and already small inaccuracies of the used linear registration may explain apparent inconsistencies with our data.

As noted, 9 of 10 of our patients with central post-stroke pain of thalamic origin had a lesion of the ventral posterior nucleus. It is interesting that 8 of 10 control subjects also had lesions of the ventral posterior nucleus without developing central post-stroke pain of thalamic origin. This emphasizes that the specific lesion location is the critical factor putting patients at risk of developing central post-stroke pain of thalamic origin.

The voxels with the maximal lesion overlap in the patients with central post-stroke pain of thalamic origin were not affected in one of the pain patients. Interestingly, the clinical pain syndrome of this single patient is restricted to his hand, whereas the pain affects either the whole hemibody or a whole extremity in most of the other pain patients that we studied. This might explain the slight mismatch regarding the lesion location of this patient. Other possible explanations include minimal inaccuracies of the lesion location in standard stereotaxic space due to imperfect manual delineation of the volumes of interest, other inaccuracies from the non-linear transformations used to warp the MRIs to match the Colin27 MRI template, or even other minor inaccuracies inherent in the atlas definitions themselves. The applied algorithm for stereotaxic normalization, ANIMAL, has been used previously for thalamic lesion normalization in the context of postoperative evaluation of thalamotomy lesion location and volume in patients suffering from movement disorders (Atkinson et al., 2002). In addition, ANIMAL’s accuracy and ability to localize sub-nuclei and the entirety of the thalamus have been scrutinized in recent atlas-to-patient warping validation work (Chakravarty et al., 2008, 2009a, b). As non-linear registration approaches are currently believed to provide the best results when warping individual brains into standard stereotaxic space, we believe that ANIMAL is a suitable approach for the stereotaxic normalization of individual brains with thalamic lesions. However, because of interindividual anatomical variations, even non-linear methods have limitations, and an ideal normalization of brains from different subjects is impossible—simply because every brain is unique.

### Study limitations

We found that the total lesion volume was clearly larger in patients with central post-stroke pain of thalamic origin compared with the randomly chosen control subjects. This is a general problem of lesion mapping studies in which patients with deficits tend to have larger injuries than control patients without the behavioural/neurological problem (Rorden and Karnath, 2004). It must be acknowledged that this could introduce bias leading to overestimation of the odds ratio values. Moreover, more of the patients with central post-stroke pain of thalamic origin had strokes extending to extra-thalamic areas including white matter areas, although maximal odds ratio values were relatively low in these areas. That even small thalamic strokes can involve the posterior limb of the internal capsule has been reported in the past (Kim et al., 2007; Kilt et al., 2009). As a cautionary note, such white matter lesions may interfere with thalamic nuclei, sensory thalamo-cortical pathways (Seghier et al., 2005) and their function and may hence confound the results of our study. Ideally, only patients with isolated thalamic lesions would have been investigated or patients and control patients with equally sized lesions and extensions outside the thalamus. However, as patients with thalamic pain are typically an elderly population, it did not seem feasible to recruit a reasonable number of patients when restricting the inclusion criteria in this sense. Taken together, future studies are needed to confirm our findings and additional MRI measures such as diffusion tensor imaging for white matter tracking may then help to better understand the relation of white and grey matter damage.

The control patients had a follow-up of at least 2 years to minimize the likelihood that they eventually develop pain after a longer latent period. However, one of the patients with thalamic pain did not develop pain until 36 months after his stroke, and in one study, a patient developing thalamic pain 9 years after the initial lesion has been reported (Bogousslavsky et al., 1988). For practical reasons,
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