doi:10.1093/brain/awv389 BRAIN 2016: 139; 708–722 | 708

BRAIN
A JOURNAL OF NEUROLOGY

Thalamic pain: anatomical and physiological indices of prediction

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Thalamic pain is a severe and treatment-resistant type of central pain that may develop after thalamic stroke. Lesions within the ventrocaudal regions of the thalamus carry the highest risk to develop pain, but its emergence in individual patients remains impossible to predict. Because damage to the spino-thalamo-cortical system is a crucial factor in the development of central pain, in this study we combined detailed anatomical atlas-based mapping of thalamic lesions and assessment of spinothalamic integrity using quantitative sensory analysis and laser-evoked potentials in 42 thalamic stroke patients, of whom 31 had developed thalamic pain. More than 97% of lesions involved an area between 2 and 7 mm above the anterior–posterior commissural plane. Although most thalamic lesions affected several nuclei, patients with central pain showed maximal lesion convergence on the anterior pulvinar nucleus (a major spinothalamic target) while the convergence area lay within the ventral posterior lateral nucleus in pain-free patients. Both involvement of the anterior pulvinar nucleus and spinothalamic dysfunction (nociceptive thresholds, laser-evoked potentials) were significantly associated with the development of thalamic pain, whereas involvement of ventral posterior lateral nucleus and lemniscal dysfunction (position sense, graphaesthesia, pallaesthesia, stereognosis, standard somatosensory potentials) were similarly distributed in patients with or without pain. A logistic regression model combining spinothalamic dysfunction and anterior pulvinar nucleus involvement as regressors had 93% sensitivity and 87% positive predictive value for thalamic pain. Lesion of spinothalamic afferents to the posterior thalamus appears therefore determinant to the development of central pain after thalamic stroke. Sorting out of patients at different risks of developing thalamic pain may be achievable at the individual level by combining lesion localization and functional investigation of the spinothalamic system. As the methods proposed here do not need complex manipulations, they can be added to routine patients' work up, and the results replicated by other investigators in the field.

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Keywords: thalamus; thalamic pain; CPSP; laser-evoked potentials; LEPs

Abbreviations: CPSP = central post-stroke pain; LEP = laser-evoked potential; SSEP = short-latency somatosensory-evoked potential; STT = spino-thalamo-cortical; VPL/M = ventral posterior lateral/medial

Received March 18, 2015. Revised November 13, 2015. Accepted November 16, 2015. Advance Access publication February 8, 2016

Introduction

Thalamic pain, first described by Dejerine and Roussy (1906), is a distressing and treatment-resistant type of central post-stroke pain (CPSP) that may develop after thalamic stroke. While 3–8% of all stroke survivors will develop CPSP (Andersen *et al.*, 1995; Klit *et al.*, 2011; O'Donnell, 2013) the figure increases to 25% in case of sensory stroke due to a thalamic lesion (Paciaroni and Bogousslavsky, 1998; Hansson, 2004), and thalamic involvement is described in about half of patients presenting with CPSP (Bowsher *et al.*, 1998; Misra *et al.*, 2008).

Thalamic pain is both a clinical challenge and a scientific mystery: it is notoriously distressing, resistant to traditional treatments, and its underlying mechanisms remain unknown. Currently, it remains impossible to predict at the individual level who will develop pain after thalamic stroke, which makes it difficult to conduct pain prevention studies by pharmacological or other treatments. Because variables such as patient age, gender and laterality of thalamic lesions have no predictive value (Klit *et al.*, 2009), attempts to predict the occurrence of this syndrome have historically focused on the anatomical location of thalamic injury. There is formal agreement that thalamic pain develops following stroke involving the territory of the geniculo-thalamic artery (Paciaroni and Bogousslavsky 1998), which conspicuously includes the principal somatosensory thalamic nucleus [ventral posterior lateral/ventral posterior medial (VPL/VPM)]. Indeed, the classical description of the thalamic syndrome by Dejerine and Roussy (1906) correlated clinical features with the pathological findings of a lesion that included 'the external nucleus of the thalamus (lateral and posterior portions especially)…'. However, after much initial focus on a lesion of the VPL complex as a determinant of thalamic pain, it became progressively clear that in many patients with VPL lesions pain never develops (Dejerine and Roussy, 1906; Garcin, 1968; Schott, 1995; Yezierski, 2002), while CPSP could arise following thalamic lesions sparing the VPL (Mauguiere and Desmedt, 1988).

A new hypothesis of thalamic pain emerged in the late 1990's, which suggested that lesions of the posterior part of the ventro-medial nucleus receiving specific lamina I projections (ventral medial posterior nucleus, VMpo) was sufficient to induce all the characteristics of thalamic pain, via disinhibition of a medial pain pathway projecting to the anterior cingulate (Craig *et al.*, 1996; Craig, 2000). Clinical-anatomical analyses by several groups, however, demonstrated later that all the classical sensory features of the thalamic syndrome, including central pain, could be produced by lesions sparing the putative location of the VMpo (Montes *et al*, 2005; Kim *et al*, 2007; Krause *et al*, 2012). In recent years, atlas-based projection of MRI lesions in humans has suggested that lesions most prone to generate thalamic pain develop at or near the border between the VPL and the anterior pulvinar nucleus. Thus, in 17 patients studied by Krause *et al.* (2012), the regions most significantly associated with thalamic pain were located within the VPL, sparing the VMpo and often extending into the anterior pulvinar nucleus, which was the only nucleus involved in three cases. Sprenger *et al.* (2012) reported that 9 of 10 patients with thalamic pain had lesions overlapping in a region labelled 'nucleus ventrocaudalis portae', which is another name for the anterior pulvinar nucleus (Table 1 in Hirai and Jones, 1989; and Lenz *et al.*, 2010; p. 126). In four patients with CPSP following small thalamic lesions, lesion mapping showed that injury was centred in the ventrocaudal nucleus, with extension to the anterior pulvinar nucleus in three of them (Kim *et al.*, 2007). Extension into the anterior pulvinar nucleus of pain-inducing thalamic lesions was also present in cases reported by Paciaroni and Bogouslavsky (1988) and by Montes *et al.* (2005; their Fig. 1B, plate A5.4).

Previous studies evaluating pain after thalamic stroke did not consider sensory signs as a predictive criterion, and absence of joint analysis of morphological and functional data was seen as a limitation (Sprenger *et al.*, 2012). Central pain is associated with abnormal thermo-nociception, and damage to the spino-thalamo-cortical (STT) system is considered crucial in the development of post-stroke thalamic pain (Boivie *et al.*, 1989; Bowsher *et al.*, 1998; Yezierski, 2002; Henry *et al.*, 2008; Klit *et al.*, 2014). Thalamic stroke most often involves several thalamic nuclei. As the STT reaches a number of lateral, posterior and medial thalamic nuclei simultaneously (Apkarian and Shi, 1994; Dum *et al.*, 2009; Bastuji *et al.*, 2015), some of which specific and others not, the anatomical localization of a thalamic lesion does not always allow inferring whether the STT transmission will be significantly affected, and physiologically-grounded prediction of central pain has been proposed on the basis of objective assessment of spinothalamic function (Garcia-Larrea *et al.*, 2002; Wasner *et al.*, 2008; Perchet *et al.*, 2013). However, single-subject prediction based on spinothalamic involvement remains also elusive: while CPSP development most often implies a lesion in the spinothalamic system, not all spinothalamic lesions lead to pain (Defrin *et al.*, 2001; Yezierski, 2002; Boivie, 2006).

Previous anatomical studies acknowledged the importance of adding spinothalamic dysfunction to the predictive workout of thalamic syndromes (Krause *et al.*, 2012; Sprenger *et al.*, 2012), but combination of neuro-functional assessment and anatomy-based prediction has not been attempted before. Therefore, in the present study we combined atlas-based localization of thalamic lesions with quantitative sensory examination and physiological recordings of spinothalamic evoked potentials [laser-evoked potentials (LEPs)] in a group of 42 thalamic stroke patients with or without central pain.

Subjects and methods

Patient recruitment

From an original set of 44 patients, two were excluded: one (with thalamic pain) because the existence of multiple bilateral lesions rendered hazardous establishing a reliable relationship between the lesions and the pain, and the other (pain free) because thalamic lesions proved of non-vascular origin. Therefore, the sample analysed here comprises 42 patients with unilateral thalamic stroke, 31 of them with CPSP of thalamic origin, and 11 not having developed CPSP. All patients had a clinical history of thalamic vascular injury with documented lesion on MRI. The mean age was 56 years (range 39–73) in patients with pain and 60 years (range 27–78) in pain-free patients [$t(40) = 1.16$; not significant]. Patients were not selected retrospectively for this work, but studied consecutively in the Neurological hospital of Lyon and the University hospital of St Etienne in 2001–15. The distribution of patients with and without CPSP in this series does not reflect the actual prevalence of CPSP in thalamic stroke (Paciaroni and Bogousslavsky, 1998), as patients suffering CPSP are more frequently referred to pain/neurophysiology departments for extensive investigation than those without pain. Hence, while all stroke patients benefit from clinical and radiological exams, most of those with non-painful stroke do not receive all of the quantitative and physiological investigations that were required in this study. Non-neuropathic causes of pain, including shoulder ankylosis, osteoarthritis, spasticity and contractures, which can coexist with genuine CPSP (Hansen *et al.*, 2012), were explicitly checked for in all patients. Patients not suffering CPSP could have numbness or other sensory symptoms, including paresthesiae contralateral to the thalamic lesion, but none of them had unilateral pain with neuropathic features, nor hyperalgesia or allodynia, and did not have other significant pain complaints of non-neuropathic origin, except for occasional osteoarthritis.

Demographical and clinical data of the 42 patients are summarized in Table 1. Because time between stroke and the sensory examination reported here was longer in pain than in control patients [Table 1; $t(36) = 3.6$; $P < 0.001$], we ascertained that 9 of 11 pain-free patients had remained pain-free at least 3 years after LEP recordings (telephone interviews in eight, and clinical records checked for at least 36 months in the other; delay in brackets in Table 1). In two patients with painless stroke, no follow-up data was available (one deceased) but none of them consulted again in the pain clinic.

Each of the procedures applied in this investigation can enter the routine clinical management of patients with painful stroke. Signed approval of diagnostic and treatment procedures was granted from the patients, who were always free to accept or refuse any medical procedure, including MRI. In accordance with French legislation, publication of the data collected anonymously that does not change the routine management of patients does not need to be declared or submitted to a research ethics board.

Clinical examination

All patients underwent clinical neurological examination during their visit in the neurological department and/or the pain clinic. Sensory examination integrated testing of light touch, joint position and vibration senses, graphaesthesia, superficial pain and heat sensations. Thresholds and ratings were assessed using numerical (Likert) scales, which have been shown to be superior to visual analogue scales in stroke and pain patients (Kremer *et al.*, 1981; Price *et al.*, 1999). Pain was considered as 'thalamic CPSP' when contralateral to the affected thalamus, with a neuroanatomical plausible distribution and emerging in a territory with altered sensory exam. Thalamic pain was most often of burning, and/or constrictive nature, frequently accompanied by evoked pain (allodynia/hyperalgesia), paresthesiae or summation hyperpathia (Boivie, 2006; Klit *et al*, 2011).

Lemniscal function

Standard clinical examination of at least three lemniscal submodalities (joint position sense, vibration sense, light touch) was performed in all patients but one ($n = 41$). In addition, semi-quantitative assessment of joint position sense was assessed by blind imitation of contralateral finger and toe movements, and blind search of the contralateral extremity ($n = 22$), graphaesthesia by recognition of digits drawn on the palm of the hands, forearms and feet ($n = 17$), and light touch threshold using Von Frey hairs ($n = 18$). Correct performance in four of five consecutive iterations of each test was considered normal. In addition, short-latency evoked potentials (SSEPs) were recorded using electrical, non-painful stimulation of the median nerve at the wrist and/or the tibial nerve at the ankle in 28 patients (Cruccu *et al.*, 2008). A non-cephalic reference on the shoulder contralateral to stimulus was used to record cortical and subcortical responses simultaneously (Mauguiere and Desmedt, 1988; Cruccu *et al.*, 2008). Responses were averaged online, with bandpass of 10–1500 Hz (−3 dB) over a 65 ms analysis time, at 3 kHz sampling rate. SSEP amplitudes and latencies were compared against normative data from the laboratory and from published literature (Cruccu *et al.*, 2008). Inter-side latency or amplitude asymmetries were considered significant if exceeding 2.5 standard deviation (SD) from the mean in controls; thus, amplitude drop >30% relative to the normal side was considered significant. Combined clinical and electrophysiological data allowed reliable analysis of lemniscal function in 97.6% of patients (41/42, Table 1).

Spinothalamic function

Spinothalamic function analysis concerned both negative (hypoaesthesia) and positive symptoms (allodynia, hyperalgesia). It was clinically assessed in 40 patients using discrimination of the sharp and blunt ends of a needle, temperature in tubes filled with warm or cold water, and/or cold metallic sensation of a tuning fork. In 35 of them, warm/prick perceptive and nociceptive thresholds were also quantified using thermal laser pulses. In two additional patients, thresholds were assessed using respectively a peltier probe (Thermotest, Medoc®) and a concentric planar electrode (Üçeyler *et al.*, 2013). Specific spinothalamic assessment was therefore conducted in 95% of the sample (40/42), and quantification of thresholds in 88% (37/42). Perceptive thresholds were determined as the minimal energy density giving rise to a recognizable perception for at least two of three consecutive laser stimuli. Pain threshold was determined as the minimal

Table 1 Clinical details of the 42 thalamic stroke patients

Patient	Age	Time from stroke	Pain/no pain	Main nuclei involved	SSEP abnormal	Lemniscal dysfunction	LEP abnormal	STT dysfunction
1-BEAU	69	22	Pain	VPL	ND	Yes	Yes	Yes
2-BELL	53	21	Pain	PuA, CL, MD, PuM	No	No	Yes	Yes
3-BILL	67	12	Pain	PuA, PuM, MD, CM[a]	No	No	Yes	Yes
4-BOE	53	61	Pain	PuA, VPL, LP, CL, CM, MD, PuM	Yes	Yes	Yes	Yes
5-LAM	48	50	Pain	PuA, CL, PuM	No	No	Yes	Yes
6-LAR	46	22	Pain	CL, MD	No	Yes	Yes	Yes
7-LEB	56	54	Pain	PuA, VPL, PuM	Yes	Yes	Yes	Yes
8-LEG	64	60	Pain	PuA, VPL, PuM	Yes	Yes	Yes	Yes
9-MAL	61	18	Pain	PuA, VPL, LP, CL	Yes	No	Yes	Yes
10-MAN	54	50	Pain	PuA, VPL, CL, CM, PuL[a]	No	Yes	Yes	Yes
11-MAT	70	6	Pain	PuA, VPL, LP, CM	No	No	Yes	Yes
12-PANI	53	16	Pain	PuA, VPL, VL, CM	Yes	Yes	Yes	Yes
13-PANT	65	32	Pain	PuA, VPL, LP, PuM[a]	Yes	Yes	Yes	Yes
14-PLAN	44	18	Pain	PuA, VPL, LP, PuM	ND	No	Yes	Yes
15-RIV	39	75	Pain	PuA, VPL, LP, CL, PO	No	No	Yes	Yes
16-RIVO	41	17	Pain	PuA, VPL, LP, CL, PuM	No	No	Yes	Yes
17-ROD	63	8	Pain	PuA, VPL, LP	ND	No	Yes	Yes
18-ROL	47	24	Pain	PuA, VPL, VL, CM, MD	ND	No	Yes	Yes
19-SEA	59	15	Pain	PuA, CL, PuM	Yes	Yes	Yes	Yes
20-SIL	52	9	Pain	LP, PuM[a]	No	No	No	Yes
21-THI	51	13	Pain	PuA, VPL, VL, CL, CM, MD, PuM[a]	Yes	Yes	Yes	Yes
22-HEB	62	-	Pain	PuA, CL, MD, PuM[a]	ND	ND	ND	ND
23-CONV	40	15	Pain	PuA, VPL, VL, CM, CL, PuM, VPI	ND	No	ND	Yes
24-CHER	50	-	Pain	PuA, PuM, VL, CL, CM, MD, PuM[a]	Yes	No	ND	ND
25-FORD	52	-	Pain	PuA, VPL, CL, CM, MD, PuM[a]	ND	No	ND	Yes
26-LARP	73	-	Pain	PuA, LP, CL, MD, PuM	ND	No	ND	No
27-MICH	69	84	Pain	PuA, VPL, LP, PuM	Yes	Yes	ND	Yes
28-GRIE	72	34	Pain	PuA, VPL, LP, PuM	Yes	Yes	ND	No
29-BEN	50	39	Pain	PuA, CL, PuM	Yes	Yes	No	Yes
30-CHAS	30	49	Pain	PuA, LP, CL, PuM	Yes	Yes	Yes	Yes
31-MAR	57	9	Pain	PuA, VPL, LP, CL, PuM	No	No	Yes	Yes
32-CAST	59	2 (>30)	No pain	VPL, VL, CL	Yes	Yes	No	No
33-DAV	70	3 (>30)	No pain	CL, MD	ND	No	Yes	Yes
34-DEL	40	3 (>30)	No pain	CL, MD	ND	No? ND?	No	No
35-FAR	60	2	No pain	PuA, VPL, PuM	No	No	No	No
36-LIV	58	1 (>30)	No pain	PuA, VPL, LP, VL, CM, PuM[a]	No	No	No	No
37-MICH	62	2 (>30)	No pain	VPL[b]	ND	No	No	No
38-MILL	68	4 (>30)	No pain	PuA, VPL, LP, CL, PuM	No	No	Yes	Yes
39-PINC	72	36	No pain	VPL, LP, VL[a]	Yes	Yes	No	No
40-VERM	66	6 (>30)	No pain	PuA, VPL, LP, PuM	ND	No	Yes	Yes
41-VREL	27	7 (>30)	No pain	VPL, LP, CL, PuM[a]	ND	No	Yes	Yes
42-NIC	78	8	No pain	VPL, LP, PuM	ND	No	ND	No
χ^2 *P* (Fisher)					$\chi^2 = 0.12$; n.s.	$\chi^2 = 2.74$; n.s.	$\chi^2 = 10.7$; $P < 0.005$	$\chi^2 = 14.7$; $P < 0.001$

SSEP abnormal = amplitude drop >30% relative to the non-symptomatic side and/or inter-side latency asymmetry >2.5 SD from the mean in controls. LEP abnormal = amplitude drop >30% relative to normal side and/or inter-side latency increase >30 ms (Beydoun *et al.*, 1993, Cruccu *et al.*, 2008, Garcia-Larrea *et al.*, 2010). Lemniscal dysfunction: SSEPs abnormal and/or at least two out of four lemniscal tests (joint position, graphaesthesia, vibration sense, light touch) abnormal. Spinothalamic dysfunction = LEPs abnormal and/or two out of three STT tests (heat threshold, pain threshold, hyperalgesia/allodynia) abnormal.

[a]Intralaminar (parafascicular/limitans) and/or reticularis thalami also involved.

[b]Almost all lateral nuclei involved around a core VPL lesion.

When VPL and VPM involved together only VPL is noted.

CL = central lateral; CM = central medial; Li = limitans; LP = lateral posterior; MD = medial dorsal; Pf = parafascicular; PuA = pulvinar anterior; PuL = pulvinar lateral; PuM = pulvinar medial; VA = ventral anterior; VL = ventral lateral; VPL = ventral posterior lateral; VPI = ventral posterior inferior; VPM = ventral posterior medial.

laser energy producing a pricking pain sensation, compared to pulling a hair or receiving a boiling water drop (Cruccu *et al.*, 2008). According to data from our laboratory, side-to-side differences in perceptive or nociceptive thresholds to laser were considered abnormal when exceeding 0.25 J (15 mJ/mm^2).

Nociceptive brain potentials exploring the spinothalamic transmission were recorded in 35 patients using laser stimuli (LEPs; Cruccu *et al.*, 2008; Garcia-Larrea, 2012), (data unusable in one of them due to poor signal-to-noise ratio), and in one further patient using a planar concentric electrode (Üçeyler *et al.*, 2013). Prior to LEP recordings, the patients rated verbally the intensity associated to series of ascending/descending laser pulses on a numerical scale where '1' is a barely perceptible sensation, '4' is pain threshold (a pricking sensation comparable to a drop of boiling water on the skin), and '10' intolerable pain. The stimuli used to record LEPs were those evoking a sensation 4-5/10 on the normal side, their intensity being kept identical on the affected side. LEPs were obtained using 20–32 scalp electrodes referenced to the nose, and laser pulses applied every 10 ± 2 s. Each laser pulse covered a 4-mm diameter skin spot (12.6 mm^2), and the stimulated area was slightly changed by some millimetres at each stimulation to minimize sensitisation and receptor fatigue (Cruccu *et al.*, 2008). Brain signals in response to 20–40 stimuli were averaged over a 1000 ms analysis time (100 ms of prestimulus baseline + 900 ms post-stimulus) with bandpass 0.1–100 Hz and 500 Hz sampling rate. Two runs were obtained to ensure reproducibility. Nociceptive stimulation was delivered to the most painful territory and its contralateral homologue (upper limbs in 29 patients, lower limbs in three, torso in two, and face in one patient). Latencies from stimulus onset to each of the two main LEP peaks (N2 and P2) were measured at the vertex electrode where the main waveforms culminate (Garcia-Larrea *et al.*, 2002, 2012), and the amplitudes of the same responses were calculated both from baseline and the preceding peak, following methods described previously (Garcia-Larrea *et al.*, 2002, 2010). In case of multiple peaks, latencies were estimated by extrapolating the ascending and descending branches of the component and taking the latency at their point of convergence (International Federation of Clinical Neurophysiology Societies; Goodin *et al.*, 1994). LEP amplitude ratios were calculated by dividing the amplitude to stimulation of the painful side by that obtained to stimulation of the healthy side. The latency difference between responses to stimulation of the affected and healthy sides was obtained for the two main vertex components. LEPs were considered abnormal if N2/P2 response amplitude to stimulation of the affected side was depressed by at least 30% relative to the normal side, and/or peak latency of vertex responses was delayed by at least 30 ms (Beydoun *et al.*, 1993; Garcia-Larrea *et al.*, 2010). Combined clinical and electrophysiological data allowed reliable analysis of spinothalamic function in (40/42) 95.2% of patients (Table 1).

Lesion localization

The affected thalamic nuclei were defined by superimposing MRI data onto the human thalamic atlas of Morel *et al.* (1997), following a similar procedure as previously reported (Magnin *et al.*, 2004, 2010; Montes *et al.*, 2005; Bastuji *et al.*, 2015). Contiguous axial T_1 images were available in 21 patients (14 acquired in 3D-T_1 mode). In the others T_1, T_2 and/or FLAIR axial images were used in combination. Most of the MRIs were routinely acquired in the anterior–posterior commissure (AC–PC) plane, which is the standard plane in the thalamic atlas. When it was not the case, the *x*–*y* axial plane was rotated to fit the AC–PC plane in 3D MRIs using MRIcro®. The MRI-to-Atlas superposition procedure was performed in several steps: initially by N.V., then cross-checked by M.M. who was blinded to the patients' pain status, and in a number of cases also by L.G.L. and/or an expert external to the present work, also blinded to the patients' condition (H.B.). The MRI-Atlas superposition was done in three steps. First, the level of the posterior and anterior commissures (PC–AC) in axial slices was taken as the reference (z = 0) to calculate the dorso-ventral coordinates for all other slices. Then, the slices where the thalamic lesion was visible were identified, and projected onto their *z*-corresponding axial sections in the Morel atlas. The MRI slices were scaled on the basis of AC and PC to fit the thalamic atlas, by increasing or decreasing proportionally the magnetic resonance slices to make the AC-PC distance in the MRI fit with that of the corresponding atlas plane. The best fit between the two was ensured in the postero-anterior dimension by superimposing the PC–AC levels, and in the mediolateral axis by aligning the postero-lateral thalamic borders of MRI and atlas (Kim *et al.*, 2007) and the medial border of the thalamus with the third ventricle, where contrast changes delineating the medial thalamic borders are maximal (http://neuromorphometrics.org:8080/nvm/2007-2015). Thus, anatomical relations between the lesion and the different thalamic nuclei could be established. Once the sections were superimposed, the lesions were delineated on the atlas in each individual in all available slices. In one single patient, who had a thalamic haemorrhage affecting most nuclei of the thalamus, lesion delineation could not be reliably performed because of the ambiguity of the lesion borders. The atlas slices where lesions were drawn spanned from 1.8 mm to 7.2 mm dorsal to the AC–PC plane. Comparison between the lesion localization in the 'thalamic pain' and 'pain-free' groups were performed in the slices 1.8 mm, 4.5 mm, and 7.2 mm dorsal to AC–PC, as lesions in 41/42 patients projected to at least one of these three slices, and in 36/42 patients could be mapped onto at least two of them. In one patient, the thalamic lesion was situated superior to these slices and was analysed specifically. Finally, a group map was constructed by superimposing the individual lesions of patients separately for the 'thalamic pain' and 'pain-free' groups, in each of the three slices (Fig. 3).

Data analysis

Lesion localization

The analysis of lesion sites was conducted in two complementary ways. First, the lesion outlines of each patient were superimposed on the corresponding atlas planes to delineate the thalamic regions with maximal lesion convergence (see above). This was done separately for the two groups of patients (thalamic pain and pain-free), the relative proportion of superimposed lesions involving a given thalamic area being transformed into a colour code. This approach allowed demarcating thalamic regions where lesions converged in each group, irrespective of whether they respected or not nucleus boundaries. In parallel, each thalamic nucleus received a dichotomous

classification (Yes/No) according to whether it was or not affected by the lesion in a given patient. A nucleus was considered to be affected whenever the outline of the lesion included part the nucleus in at least one atlas plane. The output of this method was the number (and percentage) of cases where a given thalamic nucleus was involved in each of the patients' groups (with pain and pain-free).

Statistical approaches

A two-way mixed-design ANOVA was used to assess perceptive and nociceptive thresholds with 'pain versus no pain' groups as between factor and 'affected side versus healthy side' as within factor. Comparison of LEP amplitudes and latencies between the sides and between the groups was done with *t*-tests. After verifying the location of the thalamic lesion convergence, possible associations between the presence of thalamic pain, sensory clinical and electrophysiological abnormalities and involvement of thalamic nuclei were tested with chi-square and Fisher's exact tests (Table 1).

A logistic regression model was constructed, whereby variables having shown independent significant chi-square associations with thalamic pain were progressively introduced as explanatory variables to optimize the predictive power of the model. Potential explanatory (independent) variables could be either objective (LEPs, SSEPs) or subjective (sensory testing, thresholds); as both of such variables could not be introduced simultaneously in the model to avoid redundancy, dichotomic variables 'lemniscal dysfunction' and 'spinothalamic dysfunction' were constructed, which combined the objective and subjective measures into a single variable before entering logistic regression. 'Lemniscal dysfunction' was considered to be present if the SSEPs and/or at least two of four lemniscal tests (joint position, graphaesthesia, vibration sense, light touch) were abnormal. Similarly 'soutpinothalamic dysfunction' was considered to be present if LEPs and/or at least one out of three STT tests (heat/pain thresholds, hyperalgesia) in the affected area were abnormal (two out of three if LEPs had not been performed).

Results

Lemniscal function

Lemniscal function could be assessed in all patients but one ($n = 41$); abnormalities were detected in 45% (14/31) of the thalamic pain patients, and in 18% (2/11) of the pain-free patients ($\chi^2 = 2.74$, not significant) (Table 1). In the 28 cases who underwent SSEPs, these were abnormal in 54% of thalamic pain patients, and in 40% of pain-free patients ($\chi^2 = 0.12$, not significant).

Spinothalamic function

Perceptive and nociceptive heat thresholds

Two-way ANOVA on nociceptive ratios in patients receiving laser pulses showed a main effect of stimulated side, with significantly increased pain thresholds to stimulation of the affected side [$F(1,33) = 19.7$; $P < 0.001$], and a significant Side × Group interaction [$F(1,33) = 8.70$; $P = 0.006$], indicating that increased pain thresholds concerned exclusively the thalamic pain group (Fig. 1). ANOVA on perceptive heat thresholds showed a main effect of both patients' group and side of stimulation [$F(1,33) = 7.50$ and 22.1, respectively; $P < 0.001$], as well as a Side × Group significant interaction indicating that the differences between healthy and affected sides were greater in the thalamic pain group [$F(1,33) = 5.57$; $P = 0.025$] (Fig. 1).

Laser-evoked potentials

In the thalamic pain patients, the vertex LEPs were attenuated on the painful side compared to healthy side [N2P2 amplitude $8.42 \pm 4.7\,\mu V$ versus $14.98 \pm 6.4\,\mu V$; $t(22) = 6.11$, $P < 0.001$]. Peak latencies of the two main components N2 and P2 were significantly delayed to stimulation of the painful compared to the healthy side (N2: 273 ± 44 ms versus 248 ± 35, $P = 0.002$; P2: 420 ± 62 ms versus 372 ± 62 ms; $P < 0.001$, paired *t*-test). In the pain-free patients, the vertex LEPs were not significantly different on symptomatic and healthy sides [$10.3 \pm 6.4\,\mu V$ versus $13.2 \pm 8.5\,\mu V$, $t(10) = -1.84$, not significant], and the peak latencies were identical to stimulation of both sides (N2: 232 ± 34 ms versus 231 ± 33 ms; P2: 356 ± 61 ms versus 358 ± 59 ms, not significant). In accordance with the above, the LEP amplitude ratio (affected versus healthy side stimulation) was significantly decreased in the thalamic pain patients, relative to the pain-free patients [0.58 ± 0.24 versus 0.86 ± 0.39; $t(29) = -2.48$, $P = 0.02$]. The N2 and P2 latency difference (affected versus healthy side stimulation) were higher in the thalamic pain patients than in pain-free patients (N2: 31 ± 35 ms versus 0.6 ± 9 ms, $P = 0.02$; P2: 51 ± 44 ms versus -2 ± 15 ms, $P < 0.001$). Figure 2 shows the grand average LEP waveforms, amplitude ratios and latency delays in both groups.

The development of thalamic pain was significantly associated with signs of altered spinothalamic function, either estimated by subjective heat thresholds ($\chi^2 = 8.97$, Fisher's exact $P < 0.01$), pain thresholds ($\chi^2 = 15.1$, Fisher's exact $P < 0.001$) or LEPs ($\chi^2 = 8.18$, Fisher's exact $P < 0.01$). Combining heat/pain thresholds and LEPs into a single variable 'spinothalamic dysfunction', further strengthened the association ($\chi^2 = 14.2$, Fisher's exact $P < 0.006$), with positive predictive value (PPV) of 86% for the presence of thalamic pain.

Lesion localization

Figure 3 shows the individual thalamic lesions superimposed on three consecutive slices of the Morel thalamic atlas (1.8, 4.5 and 7.2 mm above AC–PC level) in thalamic pain patients and in pain-free patients. In the patients with thalamic pain, maximal lesion convergence was observed in the anterior pulvinar nucleus, which received 58–64% lesion convergence in single atlas slices, and 97% incidence of anterior pulvinar nucleus involvement when combining all slices. In the pain-free patients, maximal lesion

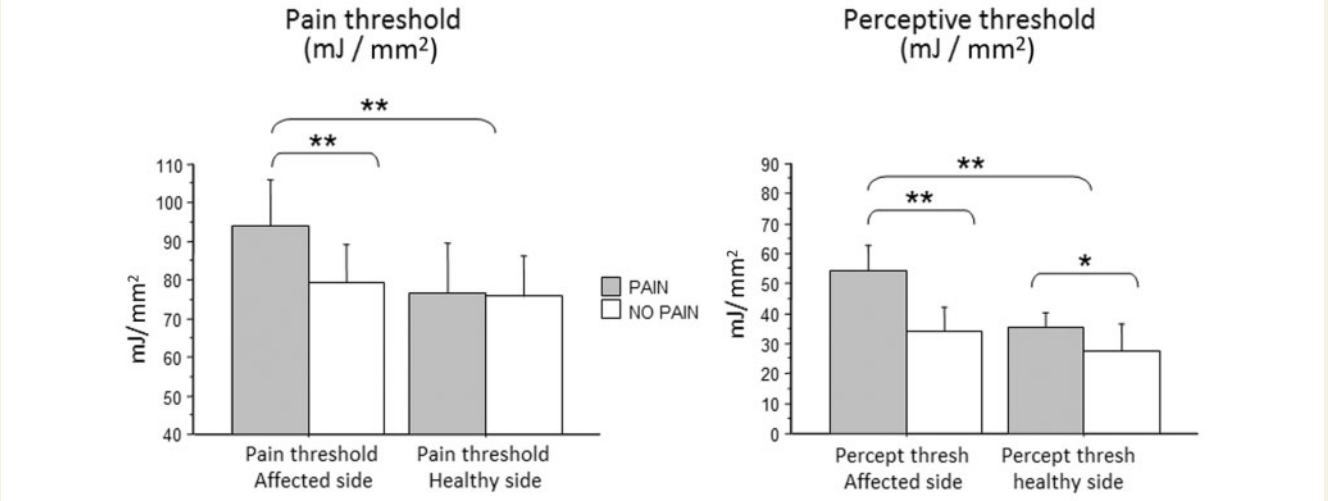

Figure 1 ANOVA interaction histograms for nociceptive and perceptive thresholds to laser pulses. Data from 35 patients in whom thresholds were assessed using laser stimuli, and expressed in mJ/mm^2. In the six other patients thresholds were either assessed clinically without quantification (n = 4) or quantified using a thermode or a concentric electrode (n = 2) and could not be pooled because of different units of measure.

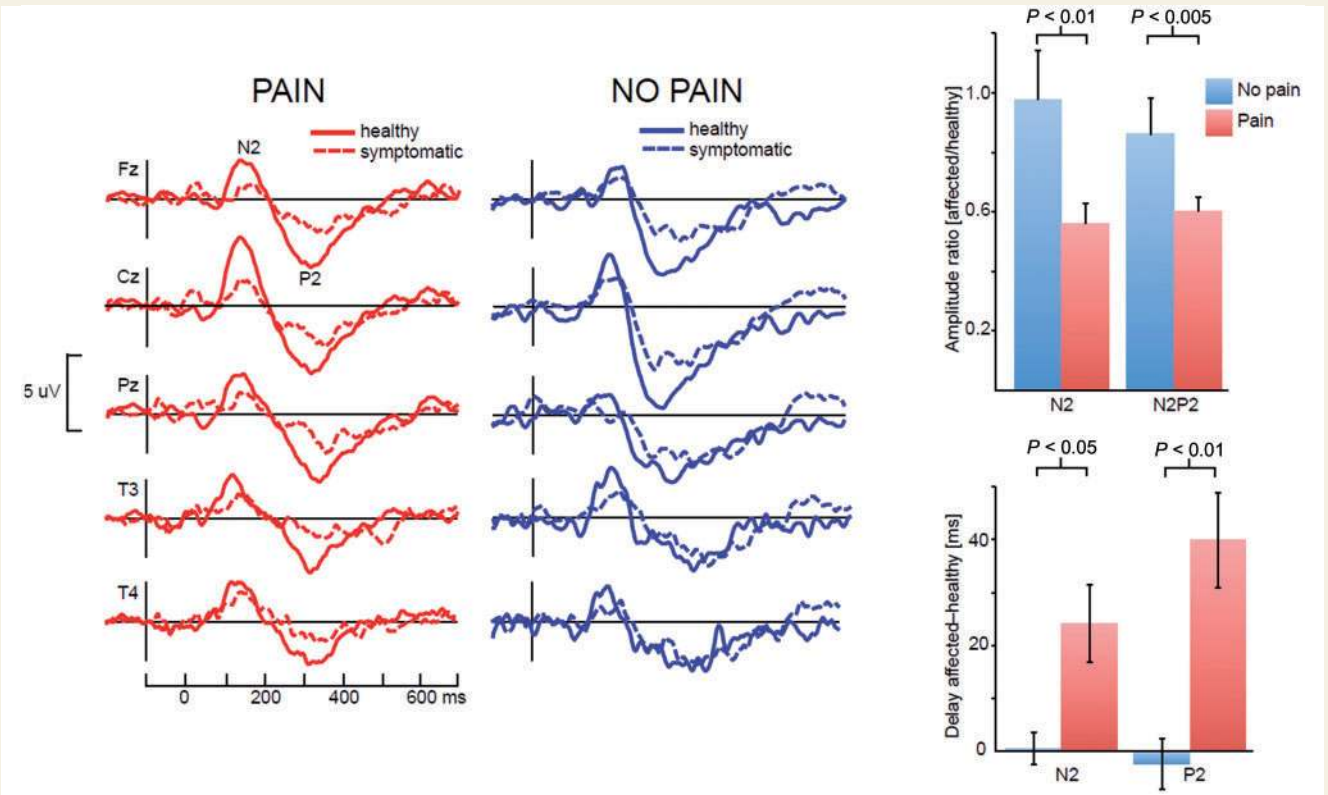

Figure 2 Grand averaged evoked potentials to nociceptive laser stimulation in patients with thalamic pain (blue) or pain free after thalamic stroke (red).

convergence was in the VPL, with 50–67% convergence in single atlas slices, and 82% incidence of VPL involvement when combining all slices. The individual thalamic nuclei most involved in both groups corresponded to the geniculostriate arterial territory, including VPL/VPM, anterior pulvinar, central lateral, medial pulvinar, lateral posterior, mediodorsal and centromedian nuclei. Parafascicular and limitans nuclei, as well as nucleus ventral posterior inferior

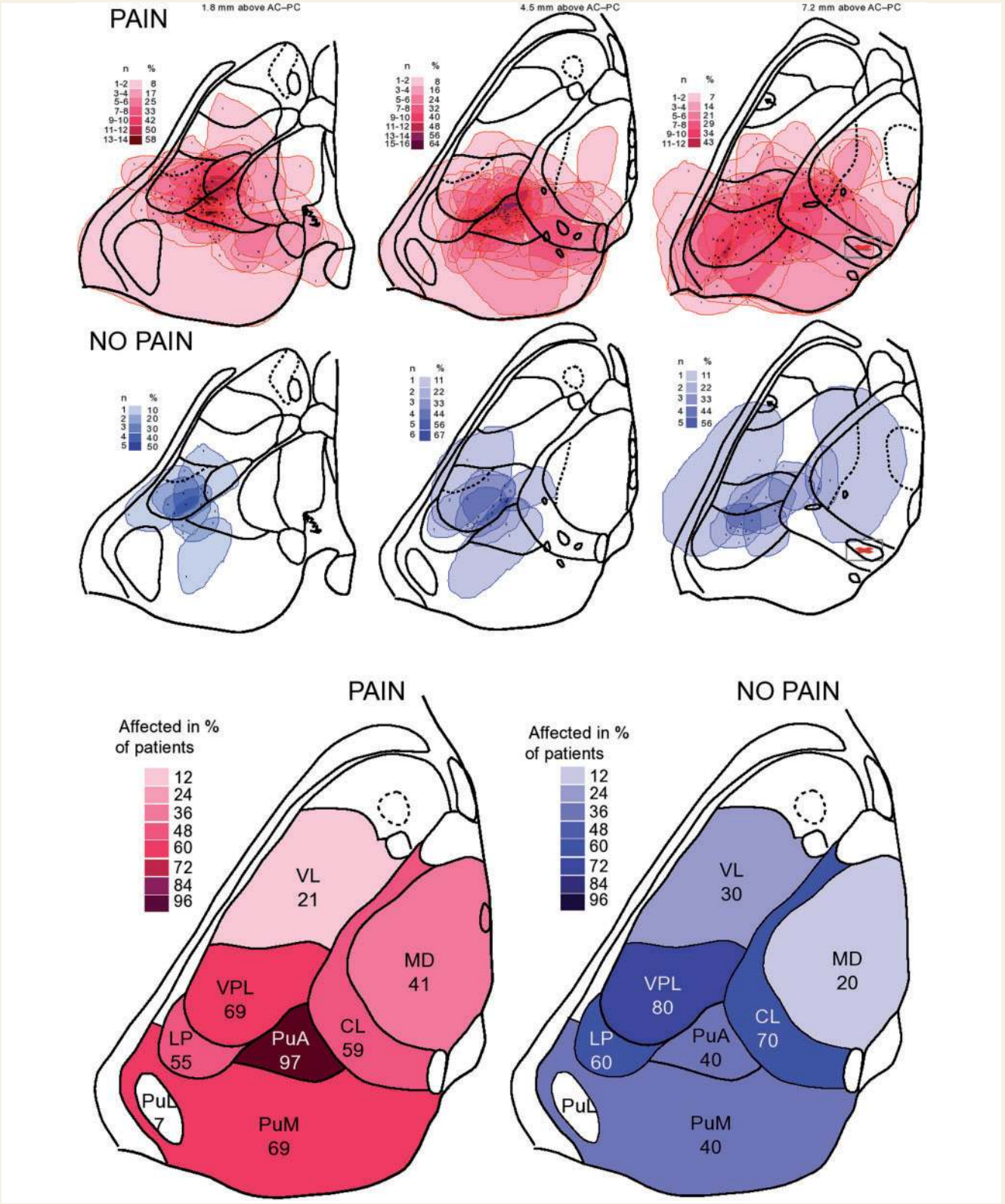

Figure 3 Lesion group maps. The two upper rows show the individual thalamic lesions for all patients superimposed on three consecutive slices of the Morel thalamic atlas (1.8, 4.5 and 7.2 mm above AC–PC level). Lesions in pain patients are illustrated in red (*top row*), and lesions in pain-free patients in blue (*second row*). The lower part of the figure shows the percentage of involvement of each major nucleus, in pain and pain-free patients. In the patients with thalamic pain (red scale), maximal lesion convergence was observed in the anterior pulvinar nucleus, which received 58–64% lesion convergence in single atlas slices, and 97% incidence of anterior pulvinar nucleus involvement when combining all slices. In the pain-free patients (blue scale), maximal lesion convergence was in the VPL, with 50–67% convergence in single atlas slices, and 82% incidence of VPL involvement when combining all slices.

and posterior complex were also involved in a minority of cases. The 'VMpo' nucleus is not indicated in current thalamic atlases; we therefore estimated its position based on the description by Blomqvist *et al.* (2000). Given its location, it could have been included in lesions involving inferio-caudal regions postero-medial to the VPL and ventral to anterior pulvinar nucleus, including the parafascicular, limitans and/or posterior complex/ventral posterior inferior nuclei, which, all taken together, were affected in a minority of patients (Table 1). One example of pain-inducing lesion depicting the location of the (unaffected) VMpo nucleus is illustrated in Fig. 4. The number of nuclei affected in thalamic pain and pain-free patients did not differ significantly [4.7 ± 2.1 versus 4.1 ± 2, $t(40) = 0.65$ not significant], and this remained so when one patient with extensive involvement of virtually all the thalamus, but no pain, was excluded from the analysis [4.7 ± 2.1 versus 3.6 ± 1.5; $t(39) = 1.49$ not significant]. Table 2 shows the frequencies of involvement for each affected thalamic nuclei.

The only nucleus showing significantly higher incidence of involvement in pain patients than pain-free subjects (87% versus 36%), and a significant association with the presence of thalamic pain was the anterior pulvinar nucleus ($\chi^2 = 9.1$; Fisher's exact $P = 0.006$). Conversely, involvement of VPL did not discriminate patients with or without pain (68% versus 82%, not significant). In seven patients with thalamic pain the VPL/VPM complex was spared while the anterior pulvinar nucleus was affected by the lesion. Figure 5 depicts electrophysiological (LEPs) and anatomical (MRI) data in four representative patients, two suffering thalamic pain and two pain free, illustrating the association between anterior pulvinar nucleus lesion, spinothalamic functional impairment and the development of thalamic pain.

Logistic regression

A logistic regression model was used to investigate whether a combination of explanatory variables would best classify patients as 'thalamic pain' or 'pain free'. The default variables introduced in the model were those having previously shown a significant individual (χ^2) association with thalamic pain—namely anterior pulvinar nucleus lesion and spinothalamic dysfunction. A model combining these two regressors yielded a correlation coefficient R = 0.687 and significant odds ratios (OR) of 20.8 for anterior pulvinar nucleus lesions [confidence interval (CI) = 1.9–227; $P = 0.012$] and 42.0 for STT dysfunction (CI 3.4–542; $P = 0.004$). The model global predictive accuracy for the development of thalamic pain was 85%, with sensitivity = 93%; specificity = 63%; PPV = 87.1%, and negative predictive value (NPV) = 77.7%.

Because lemniscal signs are common after thalamic stroke, we tested the effect of their introduction as a further regressor, even though lemniscal dysfunction was not significantly associated *per se* with thalamic pain development ($\chi^2 = 2.74$, not significant, see above and Table 1). Introducing them in the logistic model increased slightly its predictive accuracy from 87.1% to 89.9%. However, the sensitivity decreased from 93% to 89.6% when adding the lemniscal contribution, and the associated odds ratio for the contribution of lemniscal dysfunction failed to reach significance (OR = 12.04, $\chi^2 = 3.27$; CI = 0.77–700; not significant).

Discussion

Combining anatomical and functional analyses demonstrated to be a simple, yet powerful approach to detect patients at increased risk to develop pain from thalamic stroke. Both the morphological and the physiological techniques used here, including projection of MRI data onto a thalamic atlas, employed methods readily available, not needing complex equipment and that can be easily replicated by others. Anatomical (MRI) and functional indexes of spinothalamic involvement (thresholds, LEP) were independently and significantly associated with thalamic pain, and pointed to the STT lesion as a crucial element in the development of post-stroke thalamic pain. Their joint analysis proved superior to either of them alone to classify patients as 'in-pain' or 'pain-free'. Conversely, although involvement of the principal somatosensory thalamic complex (VPL/VPM nuclei) and the presence of lemniscal symptoms were also extremely common in our patients, their incidence was not significantly different in patients with or without pain, and was not associated with pain development. All in all, our findings suggest that the main determinant of central pain after thalamic stroke was the injury to spinothalamic system within the posterior thalamus.

Pain was not included as an obligatory component of the thalamic syndrome when Dejerine and Roussy (1906) introduced the term. The core syndrome included mild hemiplegia, superficial hemianaesthesia, impaired deep sensation, hemiataxia and astereognosis, and in addition could produce 'sharp, enduring, often intolerable pain' (see Schott, 1995). The present results suggest that only when the thalamic lesion implies a significant alteration of the spinothalamic system are patients likely to develop thalamic pain.

Spinothalamic dysfunction and thalamic pain

That spinothalamic dysfunction is a key feature of central pain was suggested in the late 1980's (Beric *et al.*, 1988; Boivie *et al.*, 1989; Leijon 1989). This notion has been abundantly replicated since (Bowsher *et al.*, 1998; Boivie, 2006; Henry *et al.*, 2008; Garcia-Larrea *et al.*, 2010), and hence the significant association between thalamic pain and physiological indexes of STT dysfunction in this series, although newly described, was not surprising.

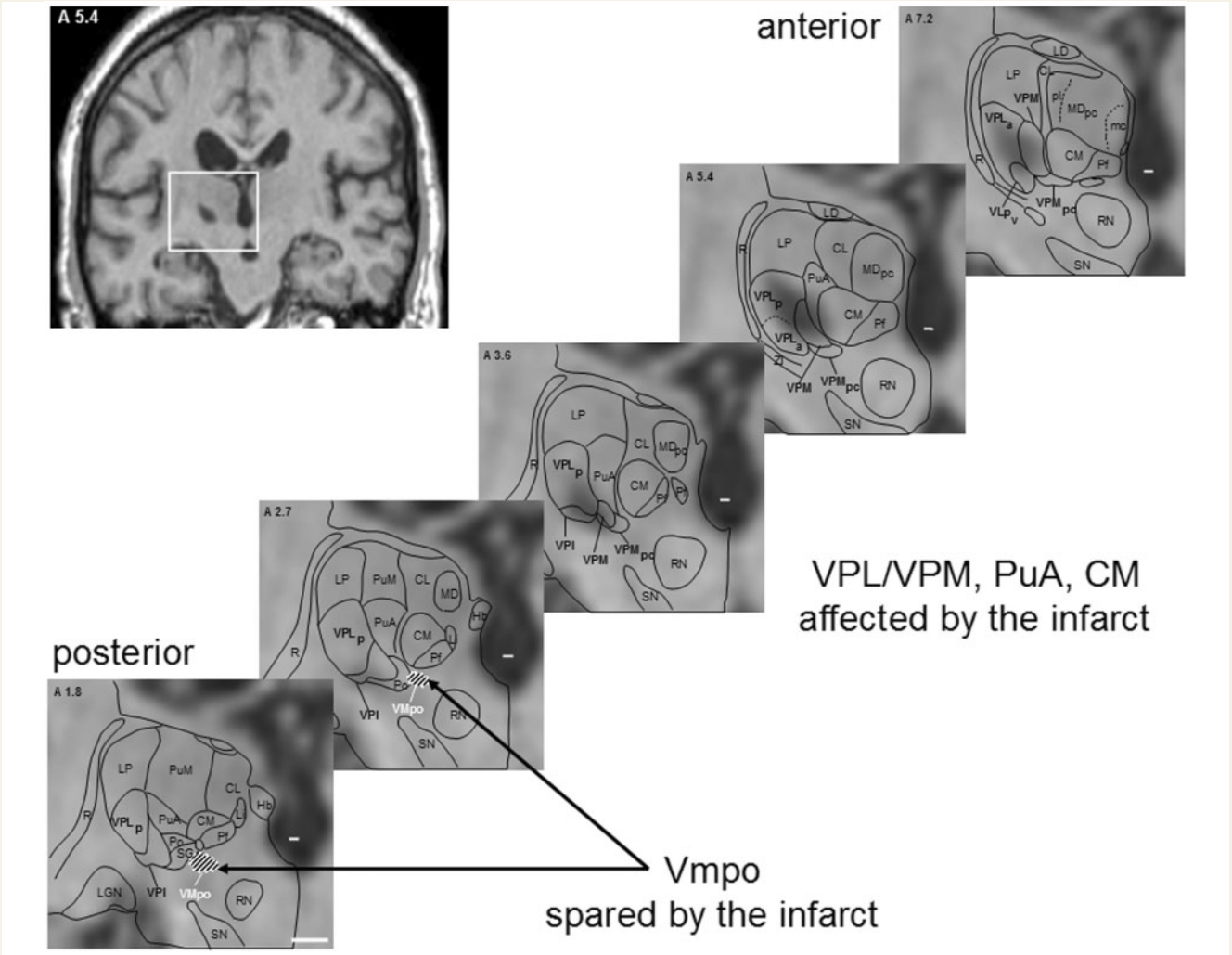

Figure 4 Localization of thalamic lesion in Patient 12. The patient suffered ischaemic thalamic stroke causing CPSP. The series of coronal slices show the ischaemic lesion involving mainly VPL/VPM, anterior pulvinar nucleus (PuA), ventro lateral posterior (VLp) and central medial (CM) nuclei, but respecting more caudally located nuclei, in particular the ventral medial posterior (VMpo; hatched). The VMpo nucleus not being included in current thalamic atlases, its location is illustrated based on data from Blomqvist *et al.* (2000).

While laser-evoked potentials have not been specifically investigated before in thalamic pain patients, they have been recorded in more varied groups of patients with stroke, and shown to be associated with CPSP (Casey *et al.*, 1996; Wu *et al.*, 1999; Garcia-Larrea *et al.*, 2002). However, spinothalamic tract lesions do not invariably lead to central pain: neurological syndromes with spinothalamic dysfunction, such as syringomyelia or Wallenberg's syndrome, only cause pain in a proportion of cases, and the clinical profiles of sensory disturbance in patients with these syndromes presenting with or without pain are very similar (MacGowan *et al.*, 1997; Ducreux *et al.*, 2006). This has led to the notion that a STT lesion may be a necessary, but not sufficient condition for central pain to develop (Defrin *et al.*, 2001) and that spontaneous activity in residual STT fibres may be crucial to maintain central pain after a spinothalamic lesion (Wasner *et al.*, 2008). In agreement with this view, STT transmission in our thalamic pain patients, as reflected by LEPs, was attenuated, delayed and/or desynchronized, but most often not abolished (Figs 2 and 4). Preliminary data have suggested that asynchrony in residual spinothalamic transmission, as reflected by time-frequency analysis of LEPs, may be predictive of central pain following a STT lesion (Perchet *et al.*, 2013).

Spinothalamic and lemniscal dysfunction coexisted in more than half of our pain patients (Table 1). This clearly differentiates thalamic stroke from other central pain syndromes such as brainstem lesions or parasylvian infarcts, where dissociated sensory loss is the rule (MacGowan *et al*, 1997; Garcia-Larrea *et al.*, 2010). Combined STT and lemniscal symptoms are common after thalamic stroke (Mauguiere and Desmedt, 1988; Wessel *et al.*, 1994; Paciaroni and Bogousslavsky, 1998), probably due to the small distance between the thalamic projections of the spinothalamic and lemniscal tracts (Bogousslavsky *et al.*, 1988). Dissociation between spinothalamic and lemniscal

Table 2 Frequencies of thalamic nuclei involvement

	Pain	Pain-free
PuA	87% (27/31)	36% (4/11)
VPL	68% (21/31)	81% (9/11)
VPM	29% (9/31)	19% (2/11)
LP	48% (15/31)	64% (7/11)
VL	19% (6/31)	36% (4/11)
CM	26% (8/31)	9% (1/11)
CL	58% (18/31)	54% (6/11)
MD	32% (10/31)	27% (3/11)
PuM	74% (23/31)	63% (7/11)
PuL	6% (2/31)	9% (1/11)
VA	-	9% (1/11)
Pf	19% (6/31)	9% (1/11)
Li	16% (5/31)	-

The values in brackets indicate the actual figures on which percentages are derived (e.g. 27/31= 87%). CL = central lateral; CM = central medial; Li = limitans; LP = lateral posterior; MD = medial dorsal; Pf = parafascicular; PuA = pulvinar anterior; PuL = pulvinar lateral; PuM = pulvinar medial; VA = ventral anterior; VL = ventral lateral; VPL = ventral posterior lateral; VPM = ventral posterior medial.

dysfunction was reported in previous series of thalamic pain (Mauguiere and Desmedt, 1988), and this was also the case in 18 patients of the present series (14 with thalamic pain), in whom abnormal LEPs, abnormal heat/pain thresholds, or both, could coexist with preserved lemniscal functions (joint position sense, graphaesthesia, vibration sense, SSEPs). Of notice, the reverse dissociation (abnormal lemniscal signs but normal STT function) was observed in one single patient with thalamic pain, thus underscoring again the different impact that spinothalamic and lemniscal dysfunction may have in determining the probability of pain after thalamic stroke.

Anterior pulvinar involvement and thalamic pain

Although the anterior pulvinar nucleus has been identified as a target of spinothalamic afferents (Jones *et al.*, 1979; Apkarian and Hodge, 1989; Rausell *et al.*, 1992; Lenz *et al.*, 2010), and its electrical stimulation in humans can evoke thermal and painful sensations (Lenz *et al.*, 1993, 2010), the possible involvement of an anterior pulvinar nucleus injury in the development of thalamic pain was not suggested until very recently. Montes *et al.* (2005) and Kim *et al.* (2007) described respectively one and four cases of thalamic pain in whom the anterior pulvinar nucleus appeared involved. Although pulvinar injuries were not a central matter of these reports, the involvement of anterior pulvinar nucleus was explicitly mentioned in two of the patients of Kim *et al.* (2007) and appears in Figure 1 of Montes *et al.* (2005). To our knowledge, the first overt recognition of a possible role of anterior pulvinar nucleus in the development of thalamic pain was due to Krause *et al.* (2012), who studied 30 patients with thalamic stroke, 18 with thalamic pain. Although the loci of maximal lesion convergence was found within the VPL, these authors underscored that the lesion cluster in pain patients affected large parts of the anterior pulvinar nucleus. They noted that 17% of patients with thalamic pain had lesions that involved the anterior pulvinar nucleus but spared the primary sensory complex (VPL/VPM), and concluded 'to a more prominent role of the anterior pulvinar' in CPSP. In the same year, Sprenger *et al* (2012) reported that lesions of 9 of 10 pain patients with thalamic pain overlapped at the border of the VPL and the pulvinar, 'coinciding with the ventrocaudalis portae nucleus', which is another label for the anterior pulvinar (a detailed correspondence of thalamic nuclei from different nomenclatures, showing the equivalence between nucleus ventrocaudalis portae and pulvinar anterior can be found in Table 1 from Hirai and Jones (1989); see also Lenz *et al.*, 2010). Our present results in 42 patients substantiate and expand these observations, and attribute a critical role to the anterior pulvinar nucleus lesions in the development of pain after thalamic stroke: not only this nucleus received 87% lesion convergence in patients with thalamic pain, but the proportion of pain patients who had a lesion involving the anterior pulvinar nucleus, but respecting the VPL/VPM, amounted to 26% (8/31). Further, and never investigated previously, the significant association between anterior pulvinar nucleus lesion and spinothalamic dysfunction underscores the role of this nucleus as a node of the human spinothalamic system, and indicates that lesion in spinothalamic projections to this nucleus puts the patient at a risk for thalamic pain.

The lack of incidence of VPL involvement in thalamic pain is intriguing, as the VPL/VPM complex also receives a fraction of spinothalamic input. The VPL was considered as the major recipient of STT afferents during most part of the 20th century, and such dogma only faltered in the 1960's, when William Mehler used the Nauta method to stain spinothalamic projections after anterolateral cordotomies in man, and suggested that the VPL/VPM thalamic nuclei 'subserve only an adjunctive function (...) in the central pain pathway' (Mehler, 1962, 1965). Subsequent projection studies in non-human primates reported less than 10% of nociceptive cells in VPL, contrasting with 50% in ventral posterior inferior (VPI) and 40% in the posterior nuclear thalamic group (Apkarian and Shi, 1994), and although other authors described more

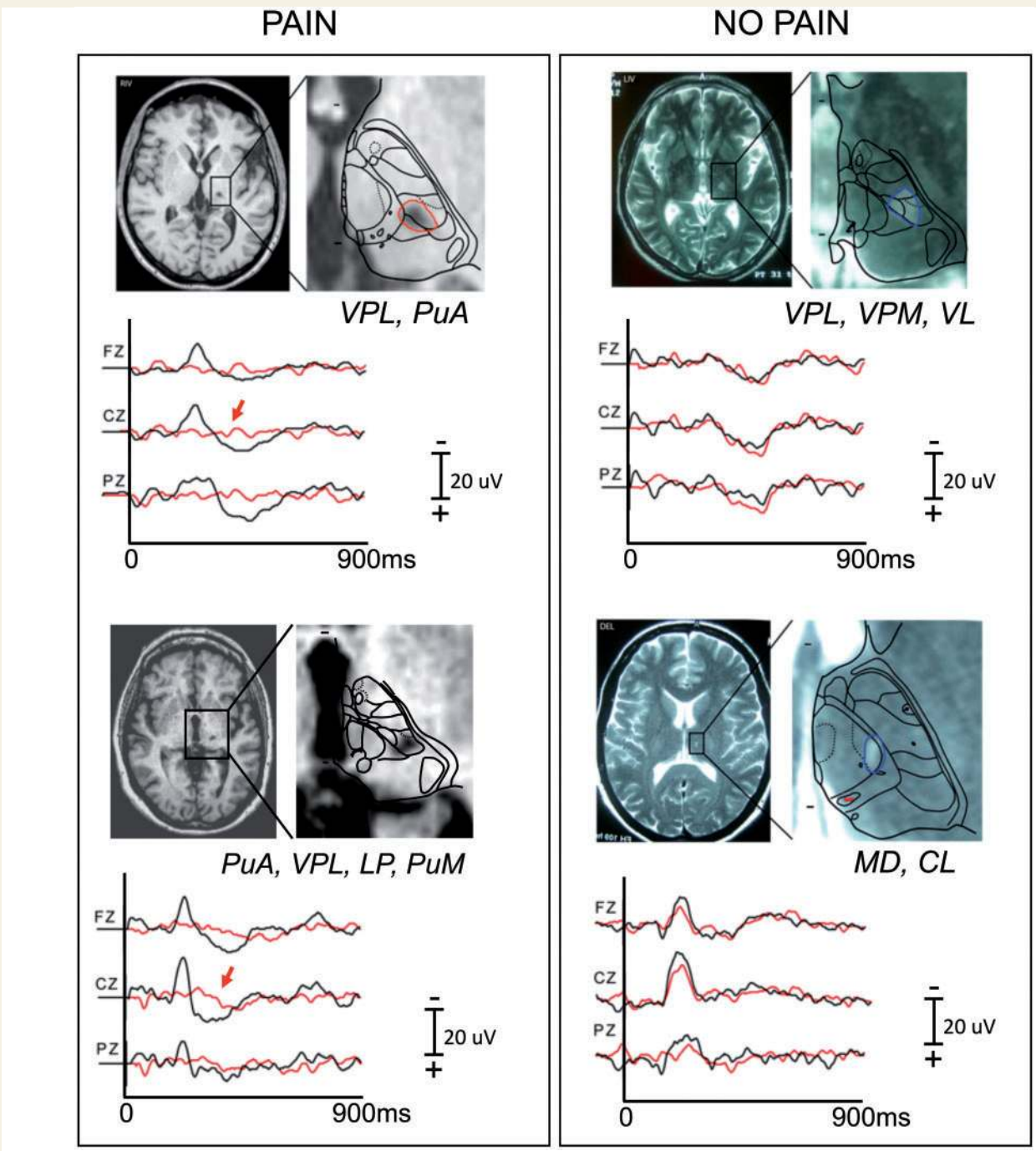

Figure 5 Anatomical lesion and spinothalamic laser-evoked potentials in four representative patients with and without thalamic pain. *Top left*: Patient RIV had an ischaemic thalamic lesion involving the VPL and the anterior pulvinar nucleus, which entailed spontaneous pain in the upper limb, lower limb and face, and allodynia in the upper limb and face. There was significant hypoaesthesia for laser heat, and LEPs were attenuated by 80% to stimulation of the affected side. There were no lemniscal symptoms and SEPs (to air pulses) were normal and symmetric. *Bottom left*: Patient PANT had presented a thalamic haemorrhage that left a hyposignal in T_1 images, involving VPL, anterior pulvinar nucleus (PuA), pulvinar medial (PuM) and lateral posterior (LP). The patient had spontaneous pain in the upper limb, lower limb, and face. There was hypoaesthesia to laser heat and pain, LEPs were 60% attenuated and SEPs were abolished. *Top right*: Patient LIV had ischaemic stroke mainly involving the VPL, VPM and ventral lateral (VL) nuclei (and slightly LP and CL, not shown in the figure) but sparing the anterior pulvinar nucleus (PuA). The patient experienced non-painful paraesthesias in the contralateral upper and lower limb. Thresholds for laser heat and pain were normal. LEPs and SEPs were normal and symmetric. *Bottom right*: Patient DEL had ischaemic thalamic lesion, affecting the medial dorsal (MD) and central lateral (CL) but sparing the main somatosensory complex (VPL/VPM) and the anterior pulvinar nucleus. The patient had transient paraesthesiae, but no pain. Thresholds to laser heat and pain were normal, and there was no lemniscal dysfunction. The LEPs were attenuated by 26–28%, which lies within normal boundaries in controls. Note that only the most representative slice is shown for each patient; some extended lesions may therefore concern nuclei not shown in the illustrated plate.

numerous VPL nociceptive projections (Willis *et al.*, 2001) only 8–25% of them corresponded to nociceptive-specific units from lamina I (Willis *et al.*, 2001, 2002; Craig, 2006). Spinothalamic projections to the VPL are rather sparse (termed 'archipelago-like', or 'islands' in Apkarian and Hodge, 1989), in contrast with the heavily concentrated rod-like projections of the lemniscal system (Rausell and Jones, 1991; Rausell *et al.*, 1992; and reviewed in Lenz *et al.* 2010; Garcia-Larrea and Magnin, 2013). All these features may sum up to determine that the probability of significant STT involvement is lesser after a lesion of VPL than a lesion involving the posterior group, of which the anterior pulvinar nucleus is a conspicuous part (Morel *et al.*, 1997; Krauth *et al.*, 2010). In this vein, local field responses to selective STT stimulation in the human VPL have been recently shown to be smaller than those recorded in the anterior pulvinar nucleus (Bastuji *et al.*, 2015).

Combining anatomical and physiological indexes

Abnormal nociceptive thresholds and LEPs, and anatomical involvement of the anterior pulvinar nucleus were all significantly and independently associated with the development of thalamic pain (Table 1). The combination of both indices increased their predictive value, both in terms of the logistic regression model accuracy and chi-squared analysis (global $\chi^2 = 22.18$; $P < 0.0001$). Such increase, although relatively modest, may represent a significant added value on clinical terms, in particular in patients who would have been incorrectly classified on one criterion only. The presence of four patients with anterior pulvinar nucleus lesions but no pain (and no STT involvement), suggests some 'threshold effect', whereby the anterior pulvinar nucleus lesion needs a given volume to induce a significant impairment of STT transmission. Thus, although our data concur with others in that the location, rather than the size of the lesion, is crucial to the development of thalamic pain (Canavero and Bonicalzi, 2007; Krause *et al.*, 2012; Sprenger *et al.*, 2012), the size may also become crucial to determine whether lesions in a given nucleus significantly intrude with STT afferents. In accordance, although the number of nuclei affected did not differ in pain patients and controls, lesions tended to be larger in the thalamic pain than in the 'no pain' group. The notion of a volume threshold may also help explain the lack of association between VPL involvement and pain development: the 'archipelago-like' structure of STT afferents to the VPL may render unlikely any significant spinothalamic impairment by small lesions restricted to this nucleus.

Limitations of the study

Although we studied our patients consecutively (i.e. they were not selected retrospectively for this work), our series was biased toward patients presenting with pain, relative to those with painless stroke. Patients suffering thalamic pain are more frequently referred to pain departments for extensive investigation than those without pain; hence, a number of non-painful stroke patients left the hospital without all the investigations needed for this project, and the series does not reflect the general prevalence of thalamic pain (Paciaroni and Bogousslavsky, 1998; Hansson, 2004). For similar reasons, patients with non-painful stroke were studied in general at a shorter delay from stroke than pain patients. Using clinical records and telephone interviews we ascertained that 9 of 11 pain-free patients had remained pain-free at least 3 years after LEP recordings, and neither of the two others came back to the pain clinic, so we considered reasonable that pain had not developed in them; however, the possibility of ultra-late development of pain in initially pain-free patients cannot be definitively ruled out. Five of our patients had lesions also outside the thalamus, which is often unavoidable in clinical studies and encountered by others (Krause *et al.*, 2012; Sprenger *et al.*, 2012). The incidence of such lesions in pain development could not be ascertained, although we believe that the numerical importance of the sample should have 'averaged out' the effect of non-thalamic lesions. Regarding methodological issues, a linear plus non-linear volumetric warping would have better matched the individual scans to the atlas than the linear coregistration procedure used here. A number of recent studies on thalamic stroke have been, however, conducted using linear coregistration methods similar to ours (Kim *et al.*, 2007; Krause *et al.*, 2012; Bastuji *et al.*, 2015). Although this may be controversial, our approach might also have some practical advantages, as the procedure of MRI/atlas projection used here does not need complex manipulations accessible only to a few specialised centres. It can be learned rapidly to be applied in routine, and despite its simplicity it has proved powerful to delineate thalamic nuclei in humans (e.g. Magnin *et al.*, 2010; Bastuji *et al.*, 2015). Our results can therefore be almost immediately replicated by other investigators in the field.

Conclusion

Likeliness of thalamic pain following thalamic stroke was estimated using relatively simple measures, namely quantitative sensory analysis and anatomical projection of MRI-based data with widely available methods. Involvement of the anterior pulvinar nucleus and impairment of pain/temperature (spinothalamic) systems were independent and significant predictors of thalamic pain, and their combination allowed a 87% positive predictive value for thalamic pain. Conversely, neither functional indices of medial lemniscus dysfunction nor VPL/VPM involvement differentiated between the thalamic pain and pain free groups. Sorting out of patients at different risks of developing thalamic pain appears therefore achievable at the individual level by combining lesion localization and objective investigation of spinothalamic

function. We should note, however, that the predictors in this study were derived from a single cohort with case-control design; future prospective designs are now necessary to validate the predictions suggested here.

Acknowledgements

We are grateful to Dr Hélène Bastuji, for useful advice and blinded cross-check of MRI-to-Atlas lesion superposition.

Funding

This work was supported by the NeuroDis Foundation (Visitor Grant to N.V.), the French Society for Pain Evaluation and Therapy (Translational Research Grant 2012-14 to L.G-L), the Laboratory of Excellence (LABEX) CORTEX (ANR-11-LABX-0042; ANR-11-IDEX-0007) in France, and by the Finnish Medical Foundation, the Jane and Aatos Erkko Foundation, the Medical Association of Pohjois-Savo in Finland.

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