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Clinical, functional and structural determinants of central pain in syringomyelia

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The present study aimed to investigate the relationship between neuropathic symptoms (i.e. pain and paraesthesia/dysaesthesia) and structural damage and functional alterations of spinal sensory tracts in patients with syringomyelia. Three-dimensional fibre tracking of the cervical spinal cord (at level C3–C4), electrophysiological assessments of nociceptive (laser-evoked potentials) and non-nociceptive (somatosensory-evoked potentials) pathways and quantitative sensory testing were carried out in 37 patients with syringomyelia, 27 with neuropathic pain and 21 controls. Four regions of the body (both hands and shoulders) were systematically examined with laser-evoked potentials and quantitative sensory testing, and somatosensory-evoked potentials were induced from both hands. The diffusion tensor imaging variables investigated included the mean fractional anisotropy, the mean apparent diffusion coefficient and the number of reconstructed nerve fibres of the tracts located within three volumes of interest (full spinal section, anterior cord and posterior cord). Consistent with the results of previous studies, patients with or without neuropathic pain were indistinguishable on the basis of quantitative sensory testing, laser-evoked and somatosensory-evoked potentials and three-dimensional fibre tracking analyses. However, in patients with neuropathic pain, higher average daily pain intensity was correlated with greater structural damage to the spinal cord, as assessed by fractional anisotropy (Spearman's $\rho = -0.64$, $P = 0.020$) and the number of reconstructed nerve fibres ($r = -0.75$; $P = 0.020$) of the full spinal cord. The number of reconstructed nerve fibres was negatively correlated with two neuropathic dimensions, i.e. 'deep spontaneous pain' ($r = -0.59$, $P = 0.040$) and 'paraesthesia/dysaesthesia' (i.e. pins and needles/tingling) ($r = -0.67$, $P = 0.020$), suggesting that various pain descriptors have distinct underlying mechanisms. Patients with both spontaneous and evoked pain clearly differed from patients with spontaneous pain only. Patients with spontaneous pain only had more severe spinal cord damage, and the correlation between average daily pain intensity and fractional anisotropy of the full spinal cord was particularly strong in this subgroup of patients (Spearman's $\rho = -0.93$, $P = 0.008$). By contrast, patients with both spontaneous and evoked pain had not only less structural spinal cord damage, but also better preserved spinothalamic and lemniscal tracts on quantitative sensory testing and electrophysiological testing. These data showed, for the first time, a direct relationship between central neuropathic pain and objective markers of spinal cord damage, and confirmed the clinical relevance of 3D fibre tracking for the sensory assessment of patients with a spinal cord lesion.

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Abbreviations: DTI = diffusion tensor imaging; FT = fibre tracking; LEP = laser-evoked potentials; SEP = somatosensory-evoked potentials

Introduction

Central neuropathic pain frequently occurs after the formation of spinal cord lesion (Siddall *et al.,* 2003; Werhagen *et al.,* 2007) and remains one of the most challenging types of pain to treat (Siddall and Middleton, 2006; Jensen and Finnerup, 2007). The mechanisms put forward to account for central pain after a spinal lesion include central sensitization (Eide *et al.,* 1996; Finnerup *et al.,* 2003*b*; Finnerup and Jensen 2004), central thermosensory disinhibition (Craig *et al.,* 2000), cortical reorganization (Wrigley *et al.,* 2009) and an imbalance between spinothalamic tracts and dorsal columns (Beric *et al.,* 1988) or spinoreticular pathways (Garcia-Larrea *et al.,* 2002). The multiplicity of mechanisms proposed probably reflects the heterogeneity of clinical phenotypes in patients. Consistent with this hypothesis, previous studies based on quantitative sensory testing, laser-evoked potentials or functional neuroimaging have suggested that patients with central pain have distinct sensory profiles (Defrin *et al.,* 2001; Garcia-Larrea *et al.,* 2002; Finnerup *et al.,* 2003*b*; Ducreux *et al.,* 2006). In addition, different responses to drug treatments as a function of the neuropathic symptoms and signs displayed by the patients have been observed in several studies (Attal *et al.,* 2000, 2002). One of the key differences between these sensory profiles seems to be the presence or absence of superimposed evoked pain (i.e. allodynia, hyperalgesia) (Garcia-Larrea *et al.,* 2002; Ducreux *et al.,* 2006). However, as most previous studies have used only one functional approach, they did not allow the determination of whether the various painful neuropathic symptoms displayed by patients with a central lesion can be linked not only with functional impairment but also with objective markers of structural changes in the spinal cord.

Recently developed imaging techniques may be more sensitive than conventional neuroimaging for the detection of changes in spinal cord structure. In particular, diffusion tensor imaging (DTI) uses MRI to evaluate the movement of extracellular water molecules within the white matter (Le Bihan, 1991). Bundles of axons form a barrier to perpendicular diffusion and a path for parallel diffusion along the nerve fibres. This makes it possible to reconstruct 3D images of white matter tracts in the spinal cord (Wheeler-Kingshott *et al.,* 2002; Ducreux *et al.,* 2005). We recently demonstrated that structural investigations of the spinal cord by 3D fibre tracking (DTI–FT) provide good objective markers of spinal somatosensory tract status in patients with spinal cord lesions related to syringomyelia (Hatem *et al.,* 2009). Solid evidence for the clinical relevance of DTI–FT is provided by the strong relationship between thermal sensory deficits (a hallmark of syringomyelia) and DTI-metrics, particularly fractional anisotropy which reflects the global architecture of fibre tracts (Müller, 2009). The use of DTI–FT to assess spinal somatosensory systems, in particular the spinothalamic tract, was supported by the relationship between fractional anisotropy and laser-evoked potentials (LEPs), which are regarded as the method of choice for evaluating spinothalamic tract function in humans (Treede *et al.,* 2003; Cruccu and Garcia-Larrea, 2004; Plaghki and Mouraux, 2005).

The present study aimed to investigate the relationship between sensory symptoms, i.e. pain and paraesthesia/dysaesthesia, and structural and functional lesions of spinal sensory tracts in patients with syringomyelia, with or without central neuropathic pain. In these patients, we carried out a combination of structural investigations of the spinal cord (DTI–FT), electrophysiological assessments of nociceptive (LEPs) and non-nociceptive (somatosensory-evoked potentials, SEPs) pathways, and quantitative sensory testing. More specifically, we attempted to determine whether the presence and/or variety of painful neuropathic symptoms displayed by patients with a central lesion could be linked with distinct functional and structural changes of the spinal cord.

Materials and methods

Subjects

We prospectively included patients from the Pain clinic and the Departments of Neurosurgery and Orthopaedics of our institutions (Ambroise Paré University Hospital, Boulogne-Billancourt, France; Kremlin-Bicêtre University Hospital, Bicêtre, France; and Cliniques universitaires St-Luc, Brussels, Belgium). All patients had a clinical history and symptoms of sensory impairment in the hands and/or shoulders, with or without neuropathic pain related to cervical, cervico-dorsal or cervico-dorso-lumbar syringomyelia (primary or associated with a chiari malformation). Syringomyelia was confirmed by spinal MRI and was stable for at least two years. Patients with other types of syringomyelia (e.g. neoplastic, traumatic) or with neurological conditions (central or peripheral) other than syringomyelia were excluded. Other exclusion criteria included major depression according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, history of major psychiatric disease, head injury, dementia, difficulty in understanding the testing procedure and being under the age of 18 years. All patients receiving neuropathic pain medication (i.e. moderate dosages of antiepileptics or tricyclic antidepressants, $n = 10$) were required to stop their treatment at least 1 week before the study. However, two patients (one with spontaneous pain only, the other with spontaneous and evoked pain) continued their treatment (gabapentin), which did not provide adequate pain relief. Rescue medication (paracetamol, tramadol, codeine) was sparingly allowed during electrophysiological and radiological evaluation.

Healthy volunteers, matched with the group of patients for age and sex, had no clinical history, clinical symptoms or signs of peripheral or CNS disorders, or abnormalities on MRI of the cervical spinal cord. None of the healthy volunteers were on medication at the time of testing or had been on medication during the month before testing.

Informed consent was obtained from all participants. The study was approved by the local institutional review boards. Each institute took care of a different aspect of the evaluation: electrophysiological testing was performed and analysed in the Université catholique de Louvain in Belgium (by S.H.), DTI at Hôpital Kremlin-Bicêtre in Paris (by D.D.) and quantitative sensory testing at Hôpital Ambroise Paré in Paris (by M.G.). Only the investigator who performed the clinical assessment (N.A.) was aware of the patients' symptoms. Patients travelled from one institution to another within a time span of 15 days.

Clinical sensory evaluation

The clinical neurological examination included a detailed description of segmental sensory deficits, as previously described (Ducreux *et al.,* 2006; Hatem *et al.,* 2009). Mechanical sensitivity tests involved an assessment of gross tactile deficits (using a cotton swab), proprioceptive deficits (joint position, stereognosis), pinprick hypoalgesia (by means of a pinwheel) and fine tactile deficits (graphaesthesia and identification of direction of movement). Thermal sensitivity was assessed with two thermorollers (Somedic Sales AB, Hörby, Sweden) at constant temperatures of 40°C (warm) and 25°C (cold), respectively. As previously described (Ducreux *et al.,* 2006), we defined an index of asymmetry of thermal sensory deficits, as the difference between the metameric extension (i.e. number of dermatomes) of heat and cold deficits on the side with maximal thermal impairment and the contralateral side.

Assessment of neuropathic symptoms and dimensions

Central neuropathic pain was considered to be present if the patients reported pain in an area of somatosensory deficit that could be directly attributed to the injury of the spinal cord, could not be related to any other condition and had specific symptomatic characteristics according to the validated Douleur Neuropathique (DN4) questionnaire (i.e. score $\geq$ 4/10) (Bouhassira *et al.,* 2005; Treede *et al.,* 2008). Patients with other types of pain (e.g. headache, musculoskeletal pain, spasticity) and who did not report neuropathic pain were included in the group of patients without pain (no pain).

Patients with neuropathic pain were asked to report their average pain intensity over the last 24 h on a 0–10 numerical rating scale, using the Brief Pain Inventory (Cleeland and Ryan, 1994). The Neuropathic Pain Symptom Inventory (Bouhassira *et al.,* 2004) was used to assess the magnitude of five neuropathic dimensions: (i) superficial burning pain; (ii) deep pain (squeezing, pressure); (iii) paroxysmal pain (electric shock-like, stabbing pain); (iv) evoked pain (on brushing, cold, heat); and (v) paraesthesia/dysaesthesia (tingling, pins and needles) in the area of maximal pain. Each dimension was rated on a numerical scale (from 0 to 10). The sensory-discriminative and affective dimensions of pain were assessed with the short-form McGill questionnaire (Melzack, 1987).

Quantitative sensory testing

Quantitative sensory tests were performed on subjects comfortably installed in a bed, in a quiet room at a constant temperature (22°C). Four regions of the body were examined: the volar surface of the two hands (C7) and the anterior surface of the two shoulders (C4). Examination sites were the same in all subjects. They were chosen because (i) cervical syringeal cavities induce neurological symptoms at the upper limbs; and (ii) an easily accessible, flat skin surface with minimal pilosity was needed for quantitative sensory testing and LEP testing. Testing order was randomized and the assessments included the determination of vibration thresholds and mechanical and thermal (warm then cold) psychophysical testing.

Vibratory stimuli were applied, at least three times, in ascending order of magnitude with a vibrameter (Somedic Sales AB) and vibration thresholds were determined by the method of limits (Lindblom and Tegner, 1979).

Detection and pain thresholds for mechanical static stimuli were assessed with calibrated von Frey hairs (0.008–300 g) (Somedic), as previously described (Bouhassira *et al.,* 1999). Care was taken to avoid stroking the skin with the hair and to apply only pressure. Subjects were asked to close their eyes during the procedure. The von Frey filaments were applied (at least twice) in ascending and descending order of stiffness. Detection thresholds were defined as the lowest pressure perceived by the subject within 3 s of the stimulus, and pain thresholds were defined as the lowest pressure considered to be painful. The force required to bend the filaments (0.008–300 g) was converted into log units.

Thermal sensations were assessed with a contact thermode (Somedic Sales AB), using the Marstock method (Fruhstorfer *et al.,* 1976). The baseline temperature of the thermode (contact surface: 25 × 50 mm) was adjusted to the subject's skin temperature. This procedure aimed to avoid a potential bias in patients with abnormal baseline skin temperatures compared with control subjects, in line with our prior study of patients with syringomyelia (Ducreux *et al.,* 2006). However, in the present study, all patients had normal skin temperatures (i.e. between 30.8 and 31.2°C) akin to healthy controls; therefore the baseline temperature was in fact 31°C in all cases. Heat and cold detection and pain thresholds were measured as previously described (Ducreux *et al.,* 2006) according to the method of limits: stimuli of increasing or decreasing intensities were applied, and for each stimulus the subjects pressed a button that reversed the thermal stimulation as soon as they detected a sensation of cold or warmth (indicating the detection thresholds) or as soon as the stimulation became painful (indicating the pain thresholds). Inter-stimulus intervals were 6–8 s for detection thresholds, 15–20 s for heat pain thresholds and 20–30 s for cold pain thresholds. The maximum temperature was set at 50°C to prevent tissue damage. The minimum temperature was set at 10°C for cold detection thresholds and 5°C for cold pain temperatures to prevent cold injury, based on previous findings (Ducreux *et al.*, 2006). The thermal rate of change was 1°C/s for detection thresholds and 2°C/s for pain thresholds. Thresholds were calculated as the means of three successive determinations and expressed as absolute values in degree Celsius.

Tactile allodynia (dynamic) in the hands and shoulders was investigated with a paintbrush (three movements) and was considered to be present if stroking the skin evoked a clear sensation of pain (Ducreux *et al.,* 2006). The intensity of allodynia was scored on a 0–10 numerical rating scale as the mean of two consecutive scores obtained at least 30 s apart. The numerical rating scale values allowed determination of the area of maximal evoked pain.

We considered allodynia to static (punctate) mechanical, hot or cold stimuli to be present if pain could be evoked with a stimulus intensity that did not produce pain in healthy controls.

Magnetic resonance imaging, diffusion tensor imaging and fibre tracking

MRI was performed on a 1.5 T MR Sonata imaging system (Siemens, Erlangen, Germany) with actively shielded magnetic field gradients

(*G* maximum, 40 mT/m). The protocol included a T_2-weighted coronal scout view followed by a sagittal T_2-weighted fast spin echo sequence (field of view, 39.9 × 39.9 cm; image matrix, 512 × 512; slice thickness, 4 mm; repetition time/echo time, 4800/114 ms). A sagittal spin-echo single-shot echo-planar parallel Grappa DTI sequence with acceleration factor 2 and 25 non-collinear non-coplanar gradient directions was then applied with 2 *b* values ($b = 0$ and 900 s/mm^2; field of view, 17.9 × 17.9 cm; image matrix, 128 × 128; 12 sections with slices thickness = 3 mm; nominal voxel size, 1.4 × 1.4 × 3 mm; repetition time/echo time, 2100/97 ms). Subjects were instructed to avoid moving the head or limbs or swallowing during the examination. The duration of the DTI scan was 4 min 37 s.

Image analysis

All MRI post-processing was performed by two experienced observers. Images were analysed voxel-by-voxel with dedicated software [DPTools (http://www.fmridools.org)], as previously described (Ducreux *et al.*, 2005).

Fibre tracking method

3D maps of fibre tracts, based on similarities between neighbouring voxels in the shape (quantitative diffusion anisotropy measures) and orientation (principal eigenvector map) of the diffusion ellipsoid, were created and coregistered (Woods *et al.*, 1998; Ulug and Van Zijl, 1999) as previously described (Facon *et al*., 2005).

MedINRIA software (http://www.sop.inria.fr/asclepios/software/MedINRIA/) was used for FT, with a fractional anisotropy threshold of 0.20.

Measurements

On the basis of findings described previously (Hatem *et al.*, 2009), for all subjects measurements were made at cervical level C3–C4, which corresponded to the upper part of the syrinx in all patients but three. These three patients (two patients with pain and one patient without) were included because although the upper limit of their spinal lesion did not extend to C4 on the MRI, their sensory deficits clearly extended above C4. Three volumes of interest were defined, each with a height of one vertebra: full spinal section, anterior cord and posterior cord. Laterolateral midlines of the cervical spinal cord were determined on the baseline diffusion (*b*0) image. DTI metrics were then determined on the 3D image. The DTI variables investigated included the mean fractional anisotropy (with normal values ~0.45) (Ciccarelli *et al.*, 2007; Van Hecke *et al.*, 2008; Müller *et al.*, 2009), the mean apparent diffusion coefficient and the number of reconstructed nerve fibres of the tracts located within the volumes of interest. Apparent diffusion coefficient maps depict Brownian motion, corresponding to the random diffusion of water molecules. In a structured medium, such as white matter tracts, water molecules diffuse along the myelin sheets of axons; diffusion is said to be anisotropic. A higher anisotropy refers to a better organized biological structure. Fractional anisotropy values of ~1 indicate full anisotropy, whereas fractional anisotropy values of ~0 indicate full isotropy (Schwartz *et al.*, 1999). The reconstructed nerve fibre is the result of 3D fibre reconstruction on the basis of similarities in diffusion properties between neighbouring voxels. It is a relative measure that does not correspond to the true number of axons that could be determined with histological analysis. Instead, this marker can be used to assess the magnitude and spatial coherence of fibre bundles (Hattingen *et al.*, 2009). The results obtained for healthy controls before the study indicated significant covariance of the reconstructed nerve fibre with body height. We therefore carried out a regression analysis with body height as an independent variable, to establish relationships between reconstructed nerve fibre and clinical measurements. We took particular care to avoid CSF partial volume effects, magnetic susceptibility effects and motion artefacts in volume of interest selection.

Somatosensory-evoked brain potentials

An EEG was recorded with 19 Ag–AgCl electrodes evenly distributed on the scalp, according to the International 10–20 system, as previously described (Hatem *et al.*, 2007). Signals were amplified and digitized (gain: 1000; filter: 0.06–75 Hz, sampling rate: 167 cps) using a PL-EEG recorder (Walter Graphtek, Germany). Signals were processed offline with BrainVision Analyser® (Brain Products GmbH, Gilching, Germany) and Letswave EEG toolbox (Mouraux, Université catholique de Louvain, Belgium). Epochs extending from 0.5 s before to 2.5 s after stimulus onset (512 bins) were bandpass filtered (0.2–25 Hz). Epochs contaminated by electrooculography were rejected on inspection by eye and were baseline-corrected (reference interval −0.5 to 0 s). Average waveforms were computed for each subject and each testing site. Reaction times to stimuli were measured as previously described (Hatem *et al.*, 2007). The upcoming stimulus was announced verbally (interstimulus interval 6–10 s). The foreperiod between the verbal warning and the stimulus varied between 0 and 2.5 s (rectangular distribution). Subjects were asked to press a hand-held micro-switch as fast as possible at the first sensation felt. The reaction time task allowed for retention of full alertness of the subjects. This was important, as the amplitude of specific LEP components may be influenced by attentional status (Treede *et al.*, 2003; Plaghki and Mouraux, 2005).

Nociceptive laser-evoked potentials

LEPs were elicited by applying stimuli to the same four sites used for quantitative sensory testing (i.e. both hands and both shoulders). The cutaneous heat stimulus was delivered by a CO_2 laser, designed and built in the Department of Physics of the Université catholique de Louvain (Plaghki *et al.*, 1994). The stimulus duration was 50 ms and the beam diameter at target was 10 mm (Hatem *et al.*, 2007). Power output was determined such that energy density was clearly supraliminal for Aδ-nociceptor activation (9.6 ± 0.9 mJ/mm^2) (Mouraux and Plaghki, 2004). For each subject, the same energy density was used at the four stimulation sites. Before beginning LEP acquisition, we measured Aδ-nociceptor and C-nociceptor activation thresholds. Threshold assessments were not recorded, to keep the number of stimuli low and the duration of the session as short as possible. Laser stimuli of increasing or decreasing energy density were applied to the dorsum of the most strongly affected hand in patients and the non-dominant hand in controls. Aδ-nociceptor and C-nociceptor activation were inferred from the reaction times of the subjects (<700 ms for Aδ-nociceptor and ≥700 ms for C-nociceptor) (Towell *et al.*, 1996; Mouraux and Plaghki, 2007). Thresholds were defined as the energy density eliciting a response in half the trials (Truini *et al.*, 2005). If patients did not perceive laser stimuli at an energy density that was clearly supraliminal for Aδ-nociceptor activation, then the highest energy density used during trials was taken as the Aδ-nociceptor and C-nociceptor activation thresholds (Finnerup *et al.*, 2003*b*). Similarly, if patients had delayed responses (≥700 ms) at an energy density that was clearly supraliminal for Aδ-nociceptor activation, then the highest energy density used during trials was retained as the Aδ-nociceptor activation threshold. For LEP recording, we carried out 30 trials at each stimulation site and sites were investigated in random order. After each stimulation block (30 trials) of the recording

session, subjects were asked to describe the sensation they perceived with the laser stimulus in their own words.

Three different components (N180, N240, P350) were characterized for each subject and each LEP waveform (Hatem *et al.,* 2007). Latencies (in milliseconds) were determined from stimulus onset to peak. LEP amplitude was measured from the N240 peak to the P350 peak. We constructed an index of asymmetry by dividing the difference in LEP amplitudes between the two sides of the body by the mean of right and left LEP amplitudes. We used the absolute value of this index to compare the severity of asymmetry between subjects. The value '0' indicates symmetric evoked potential amplitudes, and higher values indicate more asymmetric evoked potential amplitudes.

Non-nociceptive electrically evoked potentials

SEPs were induced in the superficial branch of the radial nerve of both hands, in order to elicit a sensation in the same skin area as with LEPs. The electrical stimulus was produced by a constant current generator (Digitimer DS7, Digitimer Ltd., United Kingdom) with stimulus parameters as previously described (Hatem *et al.,* 2007). Stimulus intensity (1.3 ± 0.4 mA) was twice the absolute detection threshold, preventing discomfort or unpleasant sensations, and was set so as to induce a non-painful sensation of tingling in the first dorsal intercarpal space. We carried out 20 trials for each hand. SEP recordings were randomly intermingled with LEP recordings. Two distinct late components (N120, P240) were characterized for each subject and within each SEP waveform (Hatem *et al.,* 2007). We constructed an electrophysiological index of asymmetry for SEPs by a method similar to that used for LEPs (see above).

Statistical analysis

Quantitative sensory testing data, electrophysiological data and DTI-metrics are expressed as means $\pm$ 1 SD. Pain assessments obtained with a numerical rating scale are expressed as medians and as 25th and 75th percentiles.

ANOVA was used for inter-group comparisons of quantitative sensory testing, electrophysiological and DTI–FT variables [with *post hoc* Bonferroni correction, as applied by PASW (Predictive Analytics SoftWare) Statistics 18 (SPSS, Chicago, USA)]. ANOVA with repeated measures analysis was carried out for data for several examination sites from the same patient (i.e. right hand, left hand, right shoulder and left shoulder). Body height was used as a covariate in statistical analyses encompassing the DTI–FT variable 'reconstructed nerve fibre'. The amplitudes of the LEP components at each stimulation site were analysed as *z*-scores with respect to mean values for healthy controls, corrected for age (Truini *et al.,* 2005). Kruskal–Wallis non-parametric tests were used for comparisons of the scores on pain questionnaires in patients with neuropathic pain.

Spearman's rank correlation coefficient (ρ) was used for bivariate correlation analysis in the groups of patients. We assessed correlations between neuropathic symptoms in the area of maximal pain (average daily pain intensity, short-form McGill questionnaire total sensory score, Neuropathic Pain Symptom Inventory dimensions) and DTI metrics (fractional anisotropy, apparent diffusion coefficient). We also assessed correlations between neuropathic symptoms in the area of maximal pain and quantitative sensory testing and electrophysiological variables measured in the same area. Multiple regression analysis with body height as an independent covariate was used to establish the relationship between neuropathic pain intensity or dimensions and the DTI–FT variable 'reconstructed nerve fibre', through the calculation of Pearson's correlation coefficient *r*.

We also separately analysed correlations between average pain intensity and DTI metrics/electrophysiological variables in patients with and without evoked pain.

The software package PASW Statistics 18 (SPSS) was used for all statistical analyses. In all cases, $P < 0.050$ was considered as significant.

Results

Subjects

We studied 37 patients with syringomyelia (46 ± 13 years; 25 female) and 21 healthy volunteers (47 ± 15 years; 13 female). All patients had mild to severe thermal (heat and/or cold) deficits of the cervicothoracic skin territories (mean dermatomal extension per hemibody: 7.2 ± 6.6) including the shoulders and/or hands in all cases. Most patients also had tactile sensory deficits, as assessed with vibration, von Frey hairs, graphaesthesia, determinations of the direction of movement, joint position or stereognosis (Table 1). The sensations elicited by the laser stimulus were described by patients as burning, sharp, shooting or stinging. Eighteen patients (49%) perceived laser stimuli at all four sites, eight patients (22%) perceived laser stimuli at three sites, four patients (11%) perceived laser stimuli at two sites, four patients (11%) perceived laser stimuli at one site and three patients (8%) did not perceive laser stimuli at all on the upper limbs. Healthy controls perceived all laser stimuli as painful and described them as burning, sharp or shooting.

Based on a thorough bedside clinical examination and the use of the DN4 questionnaire, we identified 27 patients with syringomyelia as presenting with neuropathic pain related to the syrinx (Table 1). Pain was maximal in the hand ($n = 12$) or shoulder ($n = 15$). Pain symptoms were bilateral in 10 patients and unilateral in 17 patients. In patients with unilateral pain symptoms, pain was present on the side with the most extensive thermal deficit for warmth in 14 out of 17 (82%) cases and for cold in 15 out of 17 (88%) cases. Eleven patients presented with spontaneous (continuous and/or paroxysmal) pain only, whereas 16 patients presented with both spontaneous and evoked pain; i.e. allodynia to mechanical (brush, punctate) or thermal (cold, rarely heat) stimuli. Evoked pain was present in an area of spontaneous pain (i.e. the hand or the shoulder) in all but two cases. The area of maximal evoked pain (in response to brushing, pressure or cold) coincided with that of maximal spontaneous pain in all but these two patients. The score of the 'evoked pain' dimension of the Neuropathic Pain Symptom Inventory was significantly correlated with the intensity of both average pain ($\rho = 0.62$, $P = 0.01$) and burning pain ($\rho = 0.69$, $P = 0.003$) at the same site.

Comparison of patients with and without neuropathic pain

For the comparison of outcome measures between patients with and without neuropathic pain, we initially considered all tested

Table 1 Demographic and clinical characteristics of patients

Total number of patients (*n*)	37
Age (years)	
Mean ± SD	46 ± 13
Range	21–71
Sex (M/F)	12/25
Duration of symptoms (years)	
Mean ± SD	14 ± 0.6
Range	1–40
Aetiology *n* (%)	
Chiari type I	31 (84%)
Primary	6 (16%)
Decompressive surgery (*n*, %)	25 (68%)
Syrinx localization (*n*, %)	
Cervical	1 (3%)
Cervicothoracic	29 (78%)
Cervicodorsolumbar	7 (19%)
Motor impairment (*n*, %)	13 (35%)
Thermal deficits (*n*, %)	
Symmetric	17 (46%)
Asymmetric	20 (54%)
Area of maximal thermal deficit (*n*, %)	
Shoulder (left or right)	22 (59%)
Hand (left or right)	15 (41%)
Deficits of other modalities (*n*, %)	
Vibration	23 (62%)
Tactile (von Frey hairs)	29 (78%)
Graphaesthesia	11 (30%)
Movement direction	6 (16%)
Joint position fingers	4 (11%)
Stereognosis hand	1 (3%)
Neuropathic pain (*n*, %)	27 (73%)
Spontaneous pain	11 (41%)
Spontaneous and evoked pain	16 (59%)
Brush-evoked pain	9 (33%)
Cold-evoked pain	3 (11%)
Cold- and brush-evoked pain	2 (7%)
Cold- and heat-evoked pain	1 (4%)
Cold-, heat- and brush-evoked pain	1 (4%)
Duration of pain (years)	13 ± 11
Localization of pain (*n*, %)	
Unilateral	
Hand and shoulder	8 (30%)
Hand	5 (19%)
Shoulder	4 (15%)
Bilateral	
Hands and shoulders	4 (15%)
Both hands	3 (11%)
Both shoulders	3 (11%)
Mean pain intensity median (25th–75th percentiles)	6 (4–8)
SF-MPQ tot. score median (25th–75th percentiles)	18 (10–23)
Neuropathic Pain Symptom Inventory dimensions	
Frequency	
Burning	23 (85%)
Deep	22 (82%)
Paroxysmal	16 (59%)
Evoked	20 (74%)
Paraesthesia/dysaesthesia	18 (67%)
Intensity rating median (25th–75th percentiles)	
Burning	5 (3–8)
Deep	2 (0.5–4)
Paroxysmal	2 (0–4)
Evoked	3 (0–5)
Paraesthesia/dysaesthesia	2.5 (0–5)

The duration of symptoms refers to the first symptoms of syringomyelia, i.e. subjective loss of sensation or positive sensory symptoms. Motor impairment refers to the presence of a motor deficit of the upper limbs. The classification of patients with neuropathic pain according to their pain symptoms was based on the clinical sensory examination. Assessment of pain intensity/symptoms was performed with numerical rating scales (0–10 cm) from the Brief Pain Inventory and Neuropathic Pain Symptom Inventory. Four patients with solely spontaneous pain at clinical assessment described mild pressure-evoked pain (numerical rating scales <2/10) on the Neuropathic Pain Symptom Inventory pain questionnaire. These patients were considered as having spontaneous pain. SF-MPQ = short form of the McGill Pain Questionnaire.

areas of the upper limbs, whether painful or not (i.e. both shoulders and hands). In this type of analysis (ANOVA with repeated meaures), patients with pain and patients without pain were indistinguishable on the basis of thermal/mechanical and vibration thresholds, LEPs and SEPs (Table 2). We also compared more specifically the area of maximal impairment in the hands or shoulders (generally corresponding to the area of maximal pain in patients with pain) between the two groups of patients. Again, no significant differences were observed (data not shown). DTI–FT analysis also revealed no differences between the two groups of patients (Table 3).

The only variable discriminating between patients with pain and patients without pain was the asymmetry of deficits (based on the index of asymmetry; see 'Materials and methods'). Patients with pain displayed a more asymmetric extension of thermal deficits than patients without pain ($F = 6.40$, $P = 0.020$) on clinical examination. By contrast, indices of asymmetry of LEPs and SEPs were not significantly different between the two groups of patients.

The subdivision of the group of patients with pain as a function of their symptoms confirmed the existence of a difference between patients with both spontaneous and evoked pain and patients with no pain or spontaneous pain only. The function of spinothalamic tracts of patients with spontaneous and evoked pain was better preserved in all tested areas than in patients without pain or patients with spontaneous pain only, as indicated by significantly lower thermal sensory thresholds and C-nociceptor activation threshold (Fig. 1A and B). Patients with spontaneous and evoked pain also displayed lower levels of lemniscal dysfunction than patients with spontaneous pain only or no pain, as the vibration detection thresholds of the upper limbs were significantly lower ($F = 8.04$, $P < 0.001$; *post hoc* spontaneous and evoked pain versus spontaneous pain only: $P = 0.010$ and spontaneous and evoked pain versus no pain: $P < 0.050$). Not only was the clinical somatosensory impairment milder in patients with spontaneous and evoked pain, but the DTI analyses also showed that these patients had less structural spinal cord damage than other patients (Figs 1C and 2).

Table 2 Comparisons of LEP, SEP and quantitative sensory testing in patients with neuropathic pain, patients without neuropathic pain and healthy controls

	Right hand			Left hand			Right shoulder			Left shoulder			ANOVA-RM		
	NP $n=27$	No pain $n=10$	Controls $n=21$	NP $n=27$	No pain $n=10$	Controls $n=21$	NP $n=27$	No pain $n=10$	Controls $n=21$	NP $n=27$	No pain $n=10$	Controls $n=21$	NP versus no pain	NP versus Controls	No pain versus Controls
LEP															
N240-P350 amp. (μV)	14 ± 15	11 ± 13	29 ± 16	22 ± 18	6 ± 8	30 ± 18	20 ± 19	17 ± 22	35 ± 26	22 ± 18	6 ± 8	34 ± 23	NS	**	***
N180 latency (ms)	243 ± 46	270 ± 74	198 ± 21	214 ± 51	273 ± 48	196 ± 20	213 ± 42	236 ± 53	178 ± 30	213 ± 49	257 ± 54	177 ± 28	NS	**	***
N240 latency (ms)	286 ± 59	317 ± 52	253 ± 29	256 ± 47	336 ± 63	245 ± 22	249 ± 59	253 ± 39	229 ± 35	243 ± 55	289 ± 47	231 ± 56	NS	NS	NS
P350 latency (ms)	398 ± 75	435 ± 64	396 ± 60	375 ± 82	455 ± 52	390 ± 67	358 ± 79	399 ± 42	372 ± 61	383 ± 65	421 ± 41	381 ± 51	NS	NS	NS
Reaction time (ms)	691 ± 262	631 ± 246	414 ± 84	660 ± 357	866 ± 374	401 ± 87	530 ± 203	492 ± 224	318 ± 57	527 ± 234	1021 ± 855	327 ± 65	NS	***	**
SEP															
N120-P240 amp. (μV)	40 ± 19	43 ± 13	45 ± 23	46 ± 22	42 ± 19	45 ± 24	–	–	–	–	–	–	NS	NS	NS
N120 latency (ms)	156 ± 46	131 ± 23	137 ± 28	141 ± 25	149 ± 33	142 ± 30	–	–	–	–	–	–	NS	NS	NS
P240 latency (ms)	260 ± 70	258 ± 38	277 ± 56	255 ± 61	284 ± 56	283 ± 51	–	–	–	–	–	–	NS	NS	NS
Reaction time (ms)	304 ± 104	241 ± 45	206 ± 36	285 ± 105	342 ± 180	211 ± 41	–	–	–	–	–	–	NS	NS	**
Quantitative sensory testing															
WDT (°C)	40.1 ± 7.8	39.6 ± 7.6	32.4 ± 0.5	38.2 ± 7.1	40.6 ± 7.5	32.4 ± 0.7	41.6 ± 6.8	43.1 ± 6.9	32.9 ± 1.1	39.2 ± 6.7	43.2 ± 7.2	32.7 ± 0.9	NS	***	***
CDT (°C)	21.7 ± 9.2	23.8 ± 9.7	30.8 ± 0.5	24.4 ± 8.9	22.6 ± 9.5	31.0 ± 0.4	22.8 ± 8.7	21.3 ± 9.0	30.6 ± 0.5	23.1 ± 9.4	19.8 ± 9.4	30.8 ± 0.7	NS	***	**
HPT (°C)	46.9 ± 3.4	46.0 ± 3.1	43.5 ± 2.4	44.9 ± 4.3	45.7 ± 3.9	42.9 ± 2.7	46.7 ± 2.9	48.1 ± 3.2	44.1 ± 2.1	45.5 ± 4.1	47.9 ± 2.1	43.5 ± 2.1	NS	**	**
CPT (°C)	10.7 ± 7.8	9.5 ± 5.7	11.5 ± 4.3	11.5 ± 6.9	7.4 ± 5.0	12.4 ± 5.4	9.8 ± 7.3	5.3 ± 1.0	9.5 ± 4.2	10.1 ± 7.1	6.2 ± 2.0	11.3 ± 5.8	NS	NS	NS
MDT (log N)	2.1 ± 1.0	2.3 ± 1.2	1.0 ± 0.3	2.0 ± 1.3	2.1 ± 1.3	1.0 ± 0.3	2.2 ± 1.1	2.3 ± 1.1	0.9 ± 0.1	2.5 ± 1.0	2.5 ± 0.9	1.0 ± 0.3	NS	***	***
MPT (log N)	5.3 ± 0.4	5.5 ± 0.0	5.5 ± 0.0	5.3 ± 0.4	5.4 ± 0.2	5.5 ± 0.0	5.4 ± 0.4	5.5 ± 0.0	5.5 ± 0.0	5.4 ± 0.3	5.5 ± 0.0	5.5 ± 0.0	NS	NS	NS
VDT (μm)	4.3 ± 6.0	3.1 ± 2.9	1.1 ± 0.8	5.0 ± 9.5	8.4 ± 10.9	1.2 ± 0.9	10.7 ± 11.7	12.2 ± 12.9	3.1 ± 1.3	9.0 ± 12.3	18.5 ± 14.3	3.4 ± 1.2	NS	*	*

Repeated measures ANOVA using the four sites of each patient did not show any difference between patients with NP and patients without pain (no pain). However, significant differences were observed between each patient group and healthy controls (*post hoc* Bonferroni: $*P<0.050$, $**P<0.010$ and $***P<0.001$). amp. = amplitude; WDT = warm detection threshold; CDT = cold detection threshold; HPT = heat pain threshold; CPT = cold pain threshold; MDT = mechanical (tactile punctate) detection threshold; MPT = mechanical (tactile punctate) pain threshold; NP = neuropathic pain; NS = non significant; VDT = vibration detection threshold.

Table 3 Comparisons of DTI–FT metrics: fractional anisotropy, apparent diffusion coefficient and number of reconstructed nerve fibres between patients with neuropathic pain, patients without pain and healthy controls

	Full spine			Anterior cord			Posterior cord		
	NP	No pain	Controls	NP	No pain	Controls	NP	No pain	Controls
Fractional anisotropy	0.39 ± 0.04**	0.40 ± 0.05*	0.45 ± 0.02	0.38 ± 0.06**	0.35 ± 0.09**	0.44 ± 0.02	0.39 ± 0.06**	0.39 ± 0.06*	0.46 ± 0.02
Apparent diffusion coefficient (mm^2/s)	0.94 ± 0.13	0.85 ± 0.36	0.96 ± 0.08	1.01 ± 0.16	0.89 ± 0.28	0.98 ± 0.10	0.97 ± 0.16	0.85 ± 0.26	0.93 ± 0.08
Reconstructed nerve fibres	576 ± 309**	510 ± 458**	1165 ± 424	251 ± 188***	212 ± 303**	644 ± 212	361 ± 237**	295 ± 300**	812 ± 344

Univariate ANOVA with *post hoc* Bonferroni correction showed significant differences between patients with NP and controls and no pain versus controls. No significant differences were observed between the pain and no pain groups. * $P < 0.050$, ** $P < 0.010$ and *** $P < 0.001$; NP = neuropathic pain.

Relationship between neuropathic pain intensity and markers of structural damage of the spinal cord or spinal sensory tract dysfunction

Neuropathic pain and diffusion tensor imaging–fibre tracking

In patients with neuropathic pain, higher pain intensity (average daily pain in the area of maximal pain) was associated with greater structural damage to the spinal cord, as assessed by fractional anisotropy of the full spinal cord ($\rho = -0.64$, $P = 0.020$) and of the anterior cord ($\rho = -0.57$, $P = 0.040$), and by the number of reconstructed nerve fibres of the full spinal cord ($r = -0.75$; $P = 0.020$). Significant inverse correlations were also observed between short-form McGill questionnaire total sensory score and fractional anisotropy of the full spinal cord ($\rho = -0.62$, $P = 0.030$) and of the anterior cord ($\rho = -0.61$, $P = 0.030$). The number of reconstructed nerve fibres was negatively correlated with two neuropathic dimensions, i.e. 'deep spontaneous pain' ($r = -0.59$, $P = 0.040$ for the full spine and $r = -0.66$, $P = 0.020$ for the anterior cord) and 'paraesthesia/dysaesthesia', i.e. pins and needles/tingling ($r = -0.67$, $P = 0.020$ for the full spine). No significant correlations were observed between the other neuropathic dimensions and the number of reconstructed nerve fibres ('spontaneous superficial pain': $r = 0.14$, $P = 0.645$; 'paroxysmal pain': $r = -0.35$, $P = 0.245$; 'evoked pain': $r = 0.16$, $P = 0.612$ for the full spine). No correlations were observed between pain intensity or quality and fractional anisotropy of the posterior cord or mean apparent diffusion coefficient of the full, anterior or posterior cord.

Correlations between average daily pain intensity and DTI metrics (fractional anisotropy of the full spinal cord) were particularly strong for the subgroup of patients with spontaneous pain only ($\rho = -0.93$, $P = 0.008$). In this group, there was a strong inverse correlation between the neuropathic dimension 'deep spontaneous pain' and the number of reconstructed nerve fibres of the anterior cord ($r = -0.93$, $P = 0.020$). A similar non-significant tendency was observed for correlations between DTI metrics and pain in patients with evoked pain.

Neuropathic pain and laser-evoked and somatosensory-evoked potentials

The correlations between pain intensity/symptoms and electrophysiological values were less consistent, with two exceptions. First, deep spontaneous pain in the area of maximal pain was inversely correlated with LEP amplitude measured in the same area ($\rho = -0.52$, $P = 0.005$). Second, the severity of brush-evoked pain of the hand was positively correlated with the SEP amplitude evoked on the same hand, i.e. with the preservation of lemniscal pathways ($\rho = 0.61$, $P = 0.040$).

Neuropathic pain and quantitative sensory testing

Moderate correlations were observed between short-form McGill questionnaire total sensory score and thermal thresholds of the most painful area (heat detection: $\rho = 0.58$, $P = 0.002$; cold detection: $\rho = -0.54$, $P = 0.005$; heat pain: $\rho = 0.40$, $P = 0.040$; cold

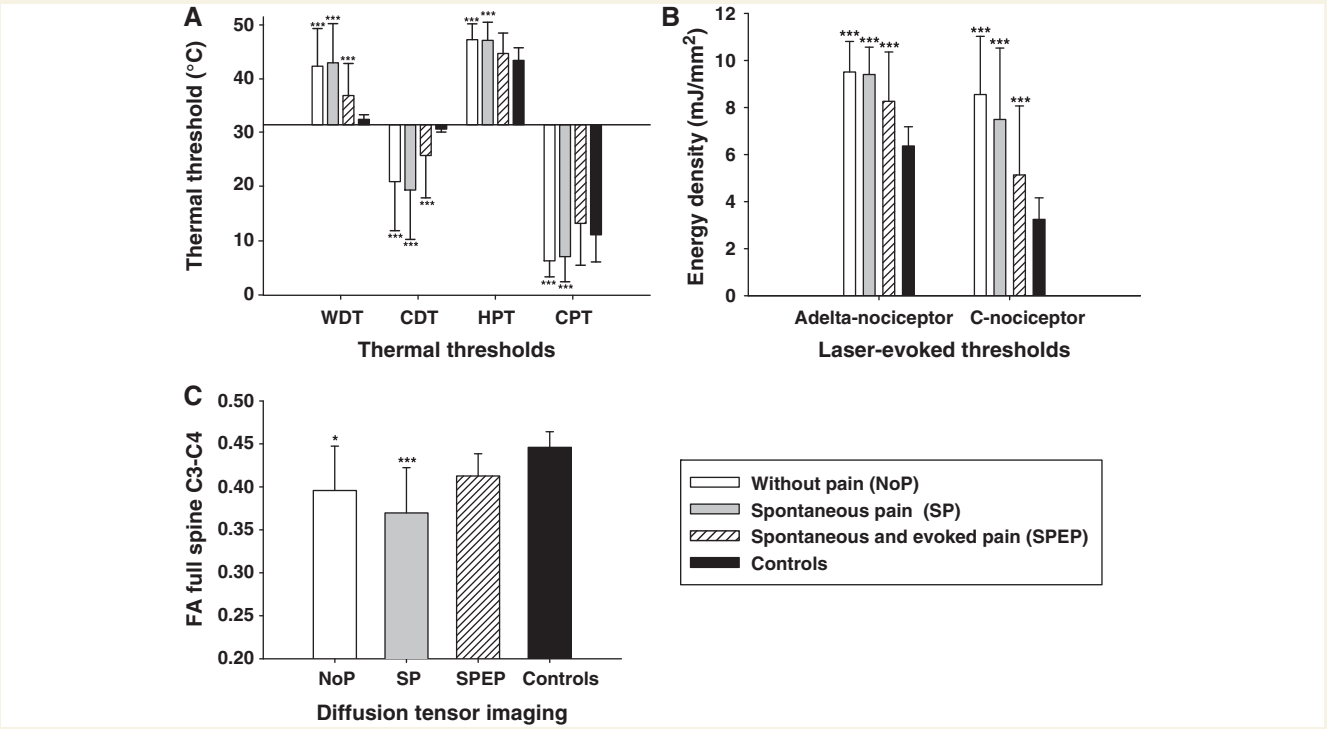

Figure 1 Comparison of spinothalamic tract function and spinal cord structure between patients with spontaneous and evoked pain (SPEP), patients with pure spontaneous pain (SP), patients without pain (NoP) and controls. Patients with spontaneous and evoked pain showed significantly fewer alterations than other patients, while no differences were observed between patients with spontaneous pain and patients without pain. (**A**) Quantitative sensory testing showed that patients with spontaneous and evoked pain had lower thermal thresholds in the upper limbs than patients without pain or patients with spontaneous pain (WDT = warm detection threshold spontaneous and evoked pain versus no pain: $P < 0.001$; spontaneous and evoked pain versus spontaneous pain: $P < 0.001$; CDT = cold detection threshold spontaneous and evoked pain versus no pain: $P = 0.003$; spontaneous and evoked pain versus spontaneous pain: $P < 0.001$; HPT = heat pain threshold spontaneous and evoked pain versus no pain: $P < 0.001$; spontaneous and evoked pain versus spontaneous pain: $P < 0.001$; CPT = cold pain threshold spontaneous and evoked pain versus no pain: $P < 0.001$; spontaneous and evoked pain versus spontaneous pain: $P < 0.001$). (**B**) Similarly, lower C-nociceptor activation thresholds indicated that patients with spontaneous and evoked pain had less spinothalamic dysfunction than other patients (spontaneous and evoked pain versus no pain: $P = 0.004$; spontaneous and evoked pain versus spontaneous pain: $P = 0.070$). (**C**) Diffusion tensor imaging showed that patients with spontaneous and evoked pain had less severe spinal cord damage than patients with spontaneous pain, as indicated by a higher fractional anisotropy (FA) of the full spinal cord at C3–C4 (spontaneous and evoked pain versus spontaneous pain: $P = 0.020$). Values are mean ± SD. ANOVA with *post hoc* Bonferroni correction for between-groups measure (shown in figure: no pain versus controls, spontaneous pain versus controls, spontaneous and evoked pain versus controls): $^{*}P < 0.050$, $^{***}P < 0.001$.

pain: non significant). In addition, the neuropathic dimension 'deep spontaneous pain' in the area of maximal pain was positively correlated with the heat pain threshold in the same area ($\rho = 0.48$, $P = 0.010$).

Discussion

In this study, we used a multimodal approach combining structural investigations of the spinal cord (DTI–FT) with electrophysiological investigations (evoked brain potentials) of nociceptive and non-nociceptive pathways and quantitative sensory testing in patients with syringomyelia, with and without neuropathic pain. We provide the first demonstration that the intensity and some of the characteristics of neuropathic pain in syringomyelia are related to objective markers of the severity of spinal cord lesions. Our data also suggest that the mechanisms of neuropathic pain associated with syringomyelia are linked to different clinical phenotypes and that DTI–FT of the spinal cord is of clinical (or diagnostic) relevance.

Relationship between neuropathic pain and markers of the severity of spinal cord damage

We previously reported a correlation between segmental sensory deficits in patients with syringomyelia and the severity of somatosensory impairment, assessed by both nociceptive LEPs and structural investigations of the spinal cord based on 3D FT (DTI–FT) (Hatem *et al.*, 2009). We show here that the intensity of average neuropathic pain and of several neuropathic dimensions, namely 'deep pain' and 'paraesthesia/dysaesthesia' (i.e. pins and needles and tingling), is correlated with several indices of structural

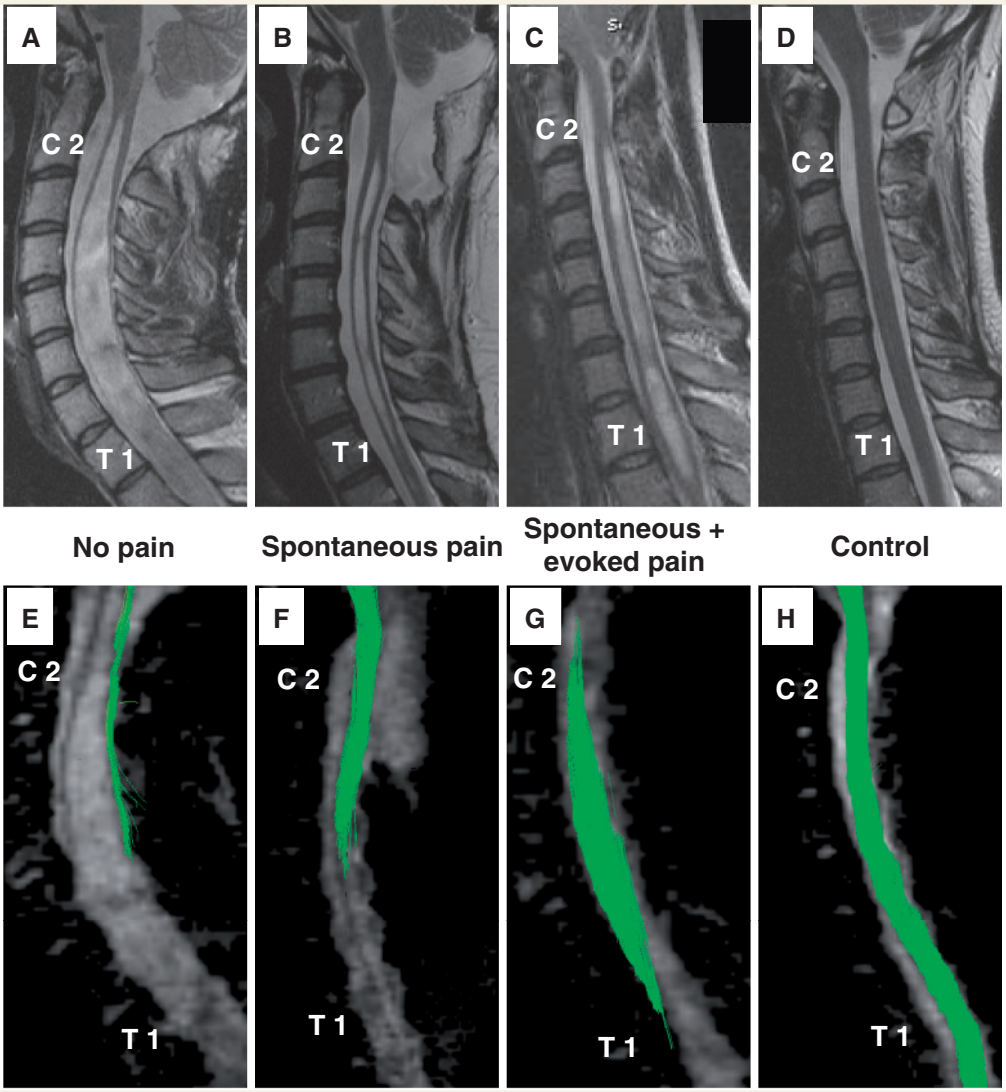

Figure 2 T_2-weighted MRIs (**A–D**) and DTI–FT (**E–H**) in three patients with syringomyelia with distinct clinical features, and in one healthy control. Images are sagittal views of the cervical spinal cord. (**A** and **E**) Twenty-four-year-old male with a syringeal cavity extending from C0 to L2. He presented with a severe thermonociceptive sensory deficit of both upper limbs. Tactile sensations were preserved. The patient had no symptoms of neuropathic pain. DTI–FT of the cervical spinal cord endorsed a severe disorganization of fibre tracts. (**B** and **F**) Thirty-six-year-old female with a syringeal cavity extending from C2 to T11. She presented with an asymmetric deficit of thermal and tactile sensations of the upper limbs, predominating on the right side. The patient had moderate spontaneous pain of the right forearm and hand (pressure, electrical discharges, paraesthesia). (**C** and **G**) A 29-year-old female with a syringeal cavity extending from C2 to T2. She presented with a thermonociceptive sensory deficit of the right C5–C8 dermatome which was maximal over the C8 radicular territory. She described severe allodynia to dynamic tactile stimuli (brush-evoked) as well as moderate burning pain and spontaneous deep pain over the C8 area of the right arm. DTI–FT of the cervical spinal cord showed a moderate disorganization of fibre tracts. (**D** and **H**) DTI–FT of the cervical spinal cord in a 34-year-old healthy female.

damage to the spinal cord, particularly in the anterior cord. Strong correlations were observed for mean fractional anisotropy and the number of reconstructed nerve fibres. The mean fractional anisotropy reflects the global anisotropy of the reconstructed fibre tracts (Van Hecke *et al.*, 2008; Cohen-Adad *et al.*, 2009; Hatem *et al.*, 2009; Müller *et al.*, 2009). These data thus suggest that the severity of structural damage to the spinal cord, involving predominantly white matter but possibly also grey matter, may influence directly the type and intensity of neuropathic pain symptoms in patients with syringomyelia. This conclusion is also supported by the link between neuropathic pain and LEPs, which reflect the activity of a nociceptive subsystem conveying the most synchronized and rapidly transmitted nociceptive and temperature afferent volleys through the lateral or neo-spinothalamic tracts in the spinal white matter (Bromm and Treede, 1987; Casey *et al.*, 1996; Garcia-Larrea *et al.*, 2002).

Interestingly, we found that the correlations between DTI metrics and pain were not identical in all subgroups of patients

with neuropathic pain. These correlations were particularly apparent in patients with spontaneous pain only. This suggests that mechanisms such as central deafferentation at the spinal or supraspinal level may account for neuropathic pain in these patients. Reorganization of the somatosensory cortex and brain connectivity changes have recently been shown to be related to neuropathic pain intensity in patients with spinal cord injury (Gustin *et al.,* 2009; Wrigley *et al.,* 2009). Patients with neuropathic pain also had more asymmetric extension of thermal sensory deficits than patients without pain, as previously described (Ducreux *et al.,* 2006). This is compatible with the idea that spontaneous pain in these patients is triggered by an imbalance in the bilateral integration of thermonociceptive information in the brain (Craig *et al.,* 2000; Ducreux *et al.,* 2006) or by an interruption of central inhibitory pathways (Milhorat *et al.,* 1996).

No significant correlations were found between DTI metrics and pain in patients with evoked pain. Furthermore, spinothalamic tract function, assessed by thermal testing and LEPs, was less impaired in these patients than in patients with spontaneous pain only, as previously reported (Garcia-Larrea *et al.,* 2002; Ducreux *et al.,* 2006; Hari *et al.,* 2009). A structural analysis of the cervical spinal cord also showed less spinal cord tissue damage in patients with evoked pain than in patients with spontaneous pain only. This finding is consistent with the results of experimental studies in animals showing stronger behavioural signs of allodynia in cases of incomplete spinal cord lesions (Siddall *et al.,* 1995). Experimental studies in patients with below-level neuropathic pain after traumatic spinal cord injury have shown that residual thermonociceptive afferents within lesioned spinothalamic tract pathways are predictive of the development of central pain (Wasner *et al.,* 2008). Neuropathic pain below the lesion has also been reported to be correlated with evoked pain at the level of the lesion in patients with traumatic spinal cord injury (Finnerup *et al.,* 2003*b*), suggesting that neuronal hyperexcitablity at injury level may be an important mechanism of below-level pain. We also observed correlations between spontaneous pain and evoked pain in our patients. The mechanisms of spontaneous and evoked pain may thus involve pathological activity of the preserved spinothalamic tract afferents, acting as 'spinal pain generators' (Wasner *et al.,* 2008). Multiple local mechanisms, including the activation of intracellular kinases (Hulsebosch *et al.,* 2009) or of microglia/astrocytes with an increase in the release of pro-inflammatory cytokines, may be involved in this process (Wasner *et al.,* 2008).

We cannot rule out the possibility that alternative central mechanisms account specifically for brush-evoked allodynia in patients with evoked pain. We found a positive correlation between brush-evoked pain and SEP amplitudes, indicating that lemniscal function was preserved. This finding is consistent with experimental studies in animals which have reported that tactile allodynia in neuropathic rats is mediated by the dorsal columns and nucleus gracilis (Sun *et al.,* 2001; however see Zhang *et al.,* 2007). It is therefore possible that brush-induced allodynia in our patients was due to supraspinal alterations in the processing of tactile stimuli, leading to central sensitization (Finnerup *et al.,* 2003*a*). It has also been suggested that neuropathic pain after spinal cord injury results from an imbalance between the impairment of spinothalamic tract and the preservation of dorsal systems (Beric *et al.,* 1988). This hypothesis is not supported by the findings reported here, since spinothalamic tract function was better preserved in patients with evoked pain than in other groups of patients. Importantly, the present study encompassed a global analysis of patients with evoked pain. However, spinothalamic and lemniscal function in these patients may vary according to the type of evoked pain. Evidence from animal studies has shown that thermal hyperalgesia and tactile allodynia are clinical manifestations of distinct pathological mechanisms (Ossipov, 2000). In patients with central post-stroke pain and cold hyperalgesia or touch allodynia, a model has been suggested in which sparing of a submodality by lesions causing central pain is associated with the occurrence of allodynia in that modality (Greenspan *et al.,* 2004; see also Defrin *et al*., 2002). Future studies comparing larger samples of patients with thermal hyperalgesia and tactile allodynia should contribute to clarify these issues.

Our data show that the mechanisms of neuropathic pain associated with a spinal cord lesion vary with symptom combinations (i.e. spontaneous and evoked pains versus spontaneous pain only). This confirms the relevance of a mechanism-based classification of neuropathic pain after central lesions and is consistent with the findings of previous studies in patients with peripheral neuropathic pain (Fields *et al.,* 1998; Baumgartner *et al.,* 2002; Baron *et al.,* 2009).

Clinical relevance of the data and methodological considerations

This study confirms the clinical relevance of a multimodal assessment of the spinal cord with LEPs, SEPs and DTI–FT evaluating not only somatosensory impairment associated with syringomyelia (Hatem *et al*., 2009) but also positive phenomena (i.e. pain, paraesthesia). Mean fractional anisotropy was the most appropriate DTI-metric marker, the apparent diffusion coefficient being much less useful. We showed previously that the apparent diffusion coefficient was also a poor marker of spinal sensory tract damage in chronic syringomyelia (Hatem *et al.,* 2009). DTI with 3D FT discriminated between subgroups of patients with pain on the basis of the severity of their spinal cord damage. The physiological variability of DTI indices between levels of the cervical spinal cord led us to choose one unique segment for investigation, C3–C4, which was the same for all subjects (Van Hecke *et al.,* 2008; Hatem *et al.,* 2009). The C3–C4 level was located in the upper part of the syrinx in all but three patients. It could be argued that the data from these three patients could have biased the present results, since the C3–C4 segment was located above the radiological upper limit of their syringeal cavity. However, these patients were included in this study because their sensory deficits clearly extended above the C4 level, suggesting that the myelopathy also extended above this level. In syringomyelia, the MRI assessment of the spinal cord allows determination of the characteristics of the syringeal cavity (size and extent), but these limits do not necessarily correspond exactly to the extent of the myelopathy induced by the syrinx (Bogdanov *et al.,* 2002, 2006). Furthermore, since we assessed sensory ascending tracts, structural damage at

levels below C3–C4 could also induce abnormal DTI–FT markers at C3–C4. DTI–FT appears to provide a better marker of pain than conventional MRI, the gold standard for detecting the presence of a syringeal cavity (Pojunas *et al.,* 1984; Tanghe, 1995), as no consistent relationship between MRI findings and sensory deficits or neuropathic pain has been identified (Arias *et al.,* 1991; Masur *et al.,* 1992, 1995; Hort-Legrand *et al.,* 1999).

Finally, this study confirms the value of LEPs for the assessment of spinothalamic tract function in patients with pain due to spinal cord injury including syringomyelia (Treede *et al.,* 1991; Garcia-Larrea *et al.,* 2002). As previously reported, changes in LEPs appeared to be more related to sensory deficits than to pain sensation, particularly in patients with evoked pain (Garcia-Larrea *et al.,* 2002; Truini *et al.,* 2009).

One limitation of the present study is that no formal correction was applied for multiple correlation analyses. Lowering the significance threshold is a way to decrease the risk of type I error, but to the detriment of a large increase of the likelihood of type II errors (Pernerger, 1998). In this exploratory study we aimed to limit the risk of false-negative results given the clinical significance of our results. Direct correlations between pain descriptors and objective markers of sensory tract damage were moderately to strongly significant from a statistical point of view, but above all exhibited a strong clinical consistency. Thus, markers of spinal cord damage were correlated not only to one, but to several measures of pain intensity or quality. Another limitation of this study is that only late SEPs could be recorded. Early SEPs are anomalous in ~90% of patients with syringomyelia (Wagner *et al.,* 1995) but cannot distinguish between a control area and the affected area in these patients (Kakigi *et al.,* 1991; Treede *et al.,* 1991). It remains possible that early cervical SEPs would provide additional information regarding the effect of lemniscal tract damage on pain patterns. Finally, the DTI–FT method used here lacked specificity in locating the spinothalamic pathways and lemniscal tracts due to the division of the spinal cord into the anterior and posterior cords. DTI studies of the spinal cord in healthy controls (Facon *et al.,* 2005) and for diseases other than syringomyelia (Ge *et al.,* 2005) have reported the successful anatomical localization of motor and/or sensory tracts, but it is difficult to discern these individual tracts in patients with syringomyelia because of the mass effect of the syrinx. Nevertheless, our findings should encourage the application of DTI–FT to other spinal conditions associated with neuropathic pain. Future longitudinal studies should also investigate the prognostic value of DTI–FT for the management and follow-up of central neuropathic pain.

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