EFNS guidelines on neuropathic pain assessment

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In September 2001, a Task Force was set up under the auspices of the European Federation of Neurological Societies with the aim of evaluating the existing evidence about the methods of assessing neuropathic pain and its treatments. This review led to the development of guidelines to be used in the management of patients with neuropathic pain. In the clinical setting a neurological examination that includes an accurate sensory examination is often sufficient to reach a diagnosis. Nerve conduction studies and somatosensory-evoked potentials, which do not assess small fibre function, may demonstrate and localize a peripheral or central nervous lesion. A quantitative assessment of the nociceptive pathways is provided by quantitative sensory testing and laser-evoked potentials. To evaluate treatment efficacy in a patient and in controlled trials, the simplest psychometric scales and quality of life measures are probably the best methods. A laboratory measure of pain that by-passes the subjective report, and thus cognitive influences, is a hopeful aim for the future.

Background and objectives

Neuropathic pain is a major disability in common neurological diseases, such as neuropathy, myelopathy, multiple sclerosis, or stroke. Pain is a complex sensation, strongly modulated by cognitive influences, and understanding nociceptive function and dysfunction is a hard task for all pain specialists. Neuropathic pain is a neurological disorder with a high prevalence, thus it is essential that neurologists get involved in its diagnosis and management. Because of lack of neurological guidelines for the assessment of neuropathic pain and its treatment, the objectives of our Task Force were to: (i) re-examine the definitions of neuropathic pain proposed by the International Association for the Study of Pain (IASP), (ii) evaluate the sensitivity of the various methods of assessing neuropathic pains (e.g. pain quality and intensity scales, quantitative sensory testing (QST), nociceptive reflexes, pain-related evoked-potentials and functional neuroimaging), (iii) evaluate the reliability of the above methods in assessing standard treatments, and (iv) propose, if necessary, new experiments that may help to clarify unsolved issues.

Search strategy

The Task Force systematically searched the Medline database from 1986 (i.e. the year when IASP published the first Classification of chronic pain), although for some issues the search went back to the 1960s and also used major textbooks and existing guidelines on some partial issues. For each specific issue, we stored all the articles sorted by the Medline search, omitted those that resulted not to be pertinent, read and rated the remaining articles according to the guidance for European Federation of Neurological Societies (EFNS) guidelines (Hughes et al., 2001), whenever applicable. In some instances, such as statements generally accepted or proved by basic neuroscience, we did not give any evidence level. The Task Force reported its results in a Consensus conference, which was held in Lisbon, 20–22 March 2003. All the European national delegates to the EFNS Panel on Neuropathic Pain were invited. Discussion groups with Task Force members and attendants resulted in a revised version, which is presented here.

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This is a Continuing Medical Education paper and can be found with corresponding questions on the Internet at: http://www.blackwellpublishing.com/products/journals/ene/mcqs. Certificates for correctly answering the questions will be issued by the EFNS.
Definitions
Neuropathic (neurogenic) pain is defined by IASP as pain caused by a lesion or dysfunction of the nervous system (Merskey and Bogduk, 1994). The IASP definition does not mention which kind of lesions. However, it is generally understood that the lesion must involve the somatosensory pathways with damage to small fibres in peripheral nerves or to the spino-thalamocortical system in the CNS. Previous classifications of neuropathic pain have been based on underlying disease (e.g. diabetic neuropathy, multiple sclerosis, etc.) or site of lesion (e.g. peripheral nerve, spinal cord, etc.). Traditionally, neurologists have considered neuropathic pains to be present only when there are definite signs of a nervous lesion. The issue about definition became even more demanding following the suggestion of a mechanism-based classification (Woolf and Max, 2001). Some characteristics of neuropathic pain such as sensitized nociceptors, allodynia, abnormal temporal summation, or extraterritorial spread of pain, are also shared by less clear chronic pain conditions (Hansson et al., 2001; Jensen et al., 2001). The inclusion of the word ‘dysfunction’ in the definition of neuropathic pain implies that other conditions such as complex regional pain syndromes or even musculoskeletal disorders associated with signs of hypersensitivity may be considered neuropathic pains. Although the narrow definition (referring to lesion) is easier to understand and complies with the current disease-based treatment indications, the broad definition (referring to dysfunction) may be rewarding for some reasons. By focusing on the mechanism, it makes clear that hyperexcitability and plasticity of the nervous system are key phenomena in chronic pain, and that treatment efficacy depends more on the underlying mechanism than aetiology (Sindrup and Jensen, 1999).

Recommendation
Testing the validity of a narrow versus a broad definition of neuropathic pain should be a major goal for future studies. In the meanwhile, however, we suggest the narrow definition and classification is retained, because of risk of overestimating neuropathic pain and because it is easy to understand (grade C recommendation).

Clinical examination and psychophysiological measures

Bedside examination
The examination of a pain patient aims at clarifying underlying disease and understanding whether the pain is nociceptive, neuropathic, psychogenic, or a combination of such. In case of neuropathic pain, abnormal sensory findings should be neuroanatomically logical, compatible with a definite lesion site.

Location, quality, and intensity of pain should be assessed. A clear understanding of the possible types of negative (e.g. sensory loss) and positive (e.g. paresthesia) symptoms and signs is necessary. Neuropathic pain can be spontaneous (stimulus-independent or spontaneous pain) or elicited by a stimulus (stimulus-dependent or stimulus-evoked pain). Spontaneous pain is often described as a constant burning sensation, but it may also include intermittent shooting, lancinating sensations, electric shock-like pain, and dysesthesias (i.e. abnormal and unpleasant sensations). Paresthesias are abnormal, although not unpleasant sensations. Stimulus-evoked pains are elicited by mechanical, thermal, or chemical stimuli. Hyperalgesia is an increased pain response to a stimulus that normally provokes pain, whereas allodynia is a pain sensation induced by a stimulus that normally does not provoke pain, and thus implies a change in the quality of a sensation. Mechanical allodynia, which is most easily tested, is further classified as dynamic (brush evoked) or static (pressure evoked).

Neurological examination in suspected neuropathic pain should include quantification and mapping of motor, sensory, and autonomic phenomena in order to identify all signs of neurological dysfunction. It is advisable to end the neurological examination with the sensory assessment. It is helpful to maintain a detailed record, preferably a diagram, of any sensory disorder to allow immediate comparison on re-testing. Although difficult for the non-specialist and time consuming for everybody, tattooing the sensory abnormality on the patient’s skin (and possibly obtaining photographic records) provides valuable information. With experience, the territory of each sensory deficit or pain can be mapped separately to reflect different areas of impairment. Tactile sense is best assessed by a piece of cotton wool, pinprick sense by a wooden cocktail-stick, thermal sense by warm and cold objects (e.g metal thermorollers), and vibration sense by a 128-Hz tuning fork (Table 1). The intensity, quality and spatial–temporal aspects of the evoked sensations should be noted, as there may be aberrations in all of them (Hansson, 1994). Standardized terms must be used in patient documents, as many cultural and medical traditions differ in the meaning of similar words (Merskey and Bogduk, 1994).

Recommendation
Although there are no validated studies on bedside examination, we emphasize that in pain patients a thorough neurological examination is invaluable – the sensory testing being the most important part of it – and is preliminary to any quantitative assessment (grade C recommendation).
The QST may be defined as the analysis of perception in response to external stimuli of controlled intensity (Table 1). Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is measured using von Frey hairs or Semmes-Weinstein monofilaments (Waylett-Rendall, 1988), pinprick sensation with weighted needles (Chan et al., 1992), and vibration sensitivity with an electronic vibrometer (Goldberg and Lindblom, 1979). Thermal perception and thermal pain are measured using a probe that operates on the Peltier principle (Fruhstorfer et al., 1976; Claus et al., 1987; Yarnitsky et al., 1995).

The QST has been used for the early diagnosis and follow-up of small fibre neuropathies that cannot be assessed by standard nerve conduction studies (see below) and its usefulness is now agreed in the early diagnosis of diabetic neuropathies (Consensus Statement; American Diabetes Association and American Academy of Neurology 1988; Peripheral Neuropathy Association 1993). QST is also particularly appropriate to quantify mechanical and thermal allodynia and hyperalgesia, which may help characterize painful neuropathic syndromes and clarify some of their pathophysiological mechanisms.

However, this method has never been used to make a differential diagnosis between neuropathic and non-neuropathic pains. Indeed QST changes are also found in non-neuropathic pain states, such as rheumatoid arthritis and inflammatory arthromyalgias (class II: Leffler et al., 2000, 2002).

The QST has been used in many trials to assess the absence of deleterious effects of treatments on sensory perception and less commonly to measure the treatment efficacy on evoked pains. Whereas most studies failed to detect treatment effects on pain thresholds in response to mechanical or thermal stimuli, treatments did significantly modulate brush-induced allodynia (intensity or area), hyperalgesia and other less common components of neuropathic pain (temporal summation, after-sensation and radiating pain). (level Ib: Marchettini et al., 1992; Watson et al., 1992; Eide et al., 1994, 1995; Belfrage et al., 1995; Rowbotham et al., 1995, 1996; Felsby et al., 1996; Pud et al., 1998; Baranowski et al., 1999; Sindrup et al., 1999; Attal et al., 2000, 2002; Wallace et al., 2000, 2002; Leung et al., 2001; Sjolund et al., 2001; Vestergaard et al., 2001).

Differential effects of treatments on allodynia/hyperalgesia in comparison with spontaneous pain and modality-specific effects have been reported (level Ib: Eide et al., 1994, 1995; Belfrage et al., 1995; Attal et al., 2000, 2002; Wallace et al., 2000, 2002; Leung et al., 2001; Sjolund et al., 2001; Vestergaard et al., 2001).

**Recommendation**

Because also found in non-neuropathic pains, QST abnormalities cannot be taken as a conclusive demonstration of neuropathic pain; furthermore QST depends on expensive equipment, it is time consuming and thus difficult to use in clinical practice (grade B recommendation). QST is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components (grade A recommendation). To evaluate mechanical allodynia/hyperalgesia, we recommend the use of simple tools such as a brush and at least one high-threshold von Frey filament. The evaluation of pain in response to thermal stimuli is best performed using the thermotest, but we do not recommend the systematic measure of thermal stimuli except for pathophysiological research or treatment trials. A simple and sensitive tool to quantify pain induced by thermal stimuli in clinical practice should be developed.

**Pain quality and intensity scales**

To assess ongoing pain, but also paroxysmal and evoked pains, the pain intensity can be measured by visual

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**Table 1** Summary of choice methods of assessing nerve function per sensation

<table>
<thead>
<tr>
<th>Fibres</th>
<th>Sensation</th>
<th>Testing</th>
<th>QST</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ</td>
<td>Touch</td>
<td>Piece of cotton wool</td>
<td>von Frey filaments</td>
<td>Nerve conduction studies, SEPs</td>
</tr>
<tr>
<td></td>
<td>Vibration</td>
<td>Tuning fork (128 Hz)</td>
<td>Vibrometer&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Aδ</td>
<td>Pinprick, sharp pain</td>
<td>Wooden cocktail stick</td>
<td>Weighted needles</td>
<td>Nociceptive reflexes, LEPs</td>
</tr>
<tr>
<td>Cold</td>
<td>Thermorollers</td>
<td>Thermotest&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>–</td>
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<tr>
<td>C</td>
<td>Warmth</td>
<td>Thermorollers</td>
<td>Thermotest&lt;sup&gt;b&lt;/sup&gt;</td>
<td>LEPs</td>
</tr>
<tr>
<td>Burning</td>
<td></td>
<td>–</td>
<td>Thermotest&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup>Or other device providing graded vibratory stimuli; <sup>b</sup>Or other device providing graded thermal stimuli; QST: quantitative sensory testing; SEP: somatosensory-evoked potentials; LEP: laser-evoked potentials.
analogue (VAS), numerical rating (NRS), or verbal rating (VRS) scales. VAS is one of the oldest, easiest and best validated measures to assess pain (Huskisson, 1974). Among the numerical scales the 11-point Likert scale (0 = no pain, 10 = worst possible pain) has been most widely used in recent neuropathic pain studies. In verbal rating the patients choose one of the given verbal descriptors of the intensity of pain they feel. VRS can be used for both intensity and unpleasantness. A combination of verbal and numeral rating is the Gracely Pain Scale with 13 words describing pain intensity and the numbers from 0 to 20 (Gracely et al., 1978).

The McGill Pain Questionnaire (MPQ; Melzack, 1975), and the short form of it (SF-MPQ; Melzack, 1987) are the most frequently used self-rating instruments for pain measurement and also often used in treatment trials. Both MPQ and SF-MPQ provide data on the various sensory and affective dimensions of pain, but they are not specifically designed to assess neuropathic pain and their translations in languages other than English need further validations.

Of the scales designed for neuropathic pain assessment, the Symptom Score Scale (Kvinesdal et al., 1984) has only been used in diabetic neuropathy, and the Neuropathic Pain Scale (Galer and Jensen, 1997) does not include important items such as paroxysmal pain and numbness. In addition, this scale has not been validated in neuropathic pain. Both the Leeds assessment of neuropathic symptoms and signs (LANSS scale) and Neuropathic Pain Questionnaire have been developed to differentiate neuropathic from nociceptive pain patients, rather than tools for quantitative assessment (Bennett, 2001; Krause and Backonja, 2003); these scales have only been preliminarily validated because they are recent and not yet widely used. We must still wait for a specific neuropathic pain scale that be sufficiently complete, reasonably easy, and properly validated.

Recommendation

It is recommended to rate the intensity and the unpleasantness of pain separately (Smith et al., 1998). The intensity of the different pain components that the patient may report (spontaneous ongoing pain, spontaneous paroxysmal pain, dysesthesiae and paresthesiae) or the evoked pains (allodynia and hyperalgesia), and pain worsening with movement, should be rated separately, but using the same scale. If different pain components involve different territories, these can be documented on a template body map. The simplest scales are probably the best. Whereas VRS is found easier by many patients, VAS is more apt to treatment trials because it permits parametric statistics. The 11-point Likert NRS is a good compromise (grade C recommendation).

Methods specifically designed to assess treatment efficacy

Although changes in the pain level can be and are often measured with the questionnaires or scales described above, some methods have been specifically conceived for assessing treatment efficacy, e.g. VAS for pain relief or the six-item Pain Relief Scale (Devers and Galer, 2000). As the interventions may improve the patient’s well-being also in other respects, or may have adverse effects, the validated measure Global Impression of Change (GIC) is recommended. It consists of seven verbal descriptors from ‘very much improved’ to ‘very much worse’, either reported by patient or evaluated by physician. The proportion of responders, need of rescue medication, or patient’s preference of treatment have also been used in pharmacological studies and showed their ability to reveal treatment effects in neuropathic pain.

‘Number Needed to Treat’ (NNT) (McQuay and Moore, 1998) has been used both in meta-analyses and single studies (Sindrup et al., 1999, 2003) to express how many patients should be treated to have at least 50% pain relief in one patient. A 50% pain relief has been the ‘gold standard’ criterion used in meta-analyses to calculate the NNT. With data from 2700 patients participating in a phase III study, Farrar et al. (2001) compared the 11-point Likert NRS and GIC. They found that a 50% pain reduction in the NRS corresponded to ‘very much improved’ in the GIC, whereas even a 30% reduction in the NRS was clinically important. Hence the 50% criterion for good pain relief may be too stringent.

Recommendation

All the psychometric instruments assessing treatment in neuropathic pain have been shown sensitive in several randomized controlled trials (level Ib). We recommend the use of unidimensional pain scales, particularly the VAS and pain relief scales and the evaluation of specific pain symptoms (such as burning pain, pain paroxysms, or allodynia) as this may reveal preferential effects of treatments. We do not favour the systematic use of non-specific multidimensional scales (e.g. MPQ). Although interesting, the multidimensional scales specific for neuropathic pain still lack extensive validation.

Other outcome measures

Pain reduction is most commonly used as the primary end point in the intervention studies. It is recommended to use assessment of sleep, mood, functional capacity, and quality of life (QoL) as secondary end points. Sleep can be assessed with VAS, 11-point Likert scale for
sleep interference or verbal rating (good, fair or poor). Some scales for QoL, e.g. Nottingham Health Profile (NHP), also assess sleep. The Beck Depression Scale (Beck et al., 1961) or Zung (1965) Self-Rating Depression Scale are used to evaluate depression. For evaluation of anxiety, the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) or the State, Trait and Anxiety (Spielberg, 1975) and the Pain Anxiety Symptom Scale (McCracken et al., 1992) are available. The QoL scales NHP and SF-36 Health Survey (SF-36) also evaluate mood.

The functional capacity (physical, cognitive, emotional and social) of the neuropathic patient can be impaired by the underlying neurological disease, sensory disturbances and treatment. The Sickness Impact Profile, a generic measure of functional status (Follick et al., 1985) has been used for neuropathic pain patients.

Improvement of QoL is regarded as the final aim of pain treatment. QoL is measured either by the 11-point scale or by specific scales such as SF-36 (Ware and Sherbourne, 1992), NHP (Hunt et al., 1980) or QoL Index (Ferrans, 1990). In a comparison study in neuropathic pain patients, SF-36 showed a higher internal consistency reliability than NHP (Meyer-Rosberg et al., 2001a,b).

**Recommendation**

In clinical studies, QoL should be assessed with a validated and comprehensive scale such as SF-36 or NHP. Mood, sleep, anxiety, and depression, if not included in the chosen QoL measure, should be assessed separately (grade C recommendation).

**Laboratory tests**

As pain is a complex experience, strongly influenced by cultural, social and emotional factors, it would be of paramount importance to rely on techniques that provide its laboratory measure.

**Standard electrodiagnostic studies**

Large size, non-nociceptive afferents have a lower electrical threshold than small size, nociceptive afferents. Unless special techniques are adopted (experimental blocks) or specific organs are stimulated (cornea, tooth pulp and glans), electrical stimuli unavoidably also excite large, non-nociceptive afferents. The large afferent input inhibits the nociceptive input at central synapses and hinders the nociceptive signals (International Federation of Clinical Neurophysiology (IFCN) Recommendations for the Practice of Clinical Neurophysiology).

**Recommendation**

Standard neurophysiological responses to electrical stimuli, such as nerve conduction studies and somatosensory-evoked potentials, are useful to demonstrate, locate, and quantify damage along the peripheral or central sensory pathways. But they do not assess function of nociceptive pathways (grade A recommendation).

**Microneurography**

Microneurography is a minimally invasive technique which allows single-fibre recordings from nerve fibres in awake subjects (Torebjork, 1993). Microneurography provides useful information on the physiology of nociceptors and their behaviour in various experimental pain models and has proved useful, by correlating abnormal discharges to perception, in understanding pathophysiology of positive sensory symptoms in neuropathic pain patients (Torebjork, 1993; Campero et al., 1996, 1998). However, microneurography is time consuming and difficult, requiring both an expert investigator and a collaborative patient; hence it is unsuitable for the clinical setting.

**Nociceptive reflexes**

The RIII flexion reflex in the biceps femoris (RIII) and the corneal reflex are purely nociceptive reflexes, in that they are exclusively mediated by nociceptive afferents and are suppressed by the antinociceptive systems and analgesic drugs (Willer et al., 1984, 1989; Willer, 1985; Cruccu et al., 1991; Sandrini et al., 2000). Although the cutaneous silent period (CSP) in the hand muscles is probably a nociceptive reflex, few studies contradict this notion and one study showed that CSP is insensitive to opiates (Serrao et al., 2001; Inghilleri et al, 2002). Although the main electrically elicited trigeminal reflexes (blink reflex and exteroceptive suppression) have been often used in pain studies, their nature is strongly controversial: evidence has been provided that large myelinated, non-nociceptive fibres predominantly contribute to these reflexes, and that these reflexes are more suppressed by benzodiazepines than opiates (class II: Cruccu et al., 1990, 1991).

As diagnostic tools, the use of the nociceptive RIII flexion reflex, corneal reflex, and CSP in neuropathic pain is extremely rare (class II: Boureau et al., 1991). The trigeminal blink reflex and exteroceptive suppression have been consistently found normal in essential trigeminal neuralgia and abnormal in trigeminal pains secondary to neuropathy, cerebello-pontine angle tumours, and multiple sclerosis (level Ia: IFCN Recommendations for the Practice of Clinical Neurophysiology).
Although the RIII reflex has been used to assess efficacy of opiates, NSAIDs, hypnosis, and neurostimulation procedures (class II: Willer, 1985; Garcia-Larrea et al., 1989, 1999; Willer et al., 1989; Bourreau et al., 1991; Sandrini et al., 2000, 2002), there is little experience in neuropathic pain patients.

Recommendation
The electrically elicited trigeminal reflexes (blink reflex and masseter inhibitory reflex) are diagnostically useful to differentiate essential trigeminal neuralgia from symptomatic trigeminal pains (grade A recommendation). The other nociceptive reflexes have little diagnostic value (grade C statement). The nociceptive reflex that is most used and appears to be most reliable in assessing treatment efficacy is the RIII flexion reflex (grade B recommendation).

Laser-evoked potentials
For many years a number of techniques have been tried for the selective activation of pain afferents. The best method now appears to be provided by radiant-heat pulse stimuli delivered by laser stimulators, which selectively excite the free nerve endings (A-delta and C) in the superficial skin layers (Bromm and Treede, 1984; Treede et al., 1995). That laser-evoked potentials (LEPs) are nociceptive responses is now widely agreed by over 100 studies. Late LEPs reflect activity of the A-delta and ultralate LEPs of the unmyelinated nociceptive pathway (Bromm and Treede, 1984, 1987, 1991; Bragard et al., 1996; Magerl et al., 1999).

Late LEPs have proved reliable in assessing damage to the peripheral and central nociceptive system in peripheral neuropathies, idiopathic and symptomatic trigeminal neuralgia, syringomelia, multiple sclerosis, Wallenberg syndrome and brain infarction (class II: Kakigi et al., 1991, 1992; Agostino et al., 2000; Cruccu et al., 2001; Garcia-Larrea et al., 2002; Truini et al., 2003). In peripheral and central neuropathic pains, LEPs are more sensitive than any other neurophysiological test and the finding of an LEP suppression helps to diagnose neuropathic pain (class II: Kakigi et al., 1992; Casey et al., 1996; Agostino et al., 2000; Garcia-Larrea et al., 2002). In fibromyalgia and myofascial syndromes, chronic fatigue syndrome, chronic inflammatory pains and psychogenic pain, LEPs have been found facilitated (mostly increased amplitude) (class II: Wendler et al., 2001; class III: Lorenz et al., 1997; Granot et al., 2001). Late LEPs are suppressed by aspirin, morphine and carbamazepine (Lorenz et al., 1997; Cruccu et al., 2001).

Ultralate LEPs related to C-fibre activation are technically more difficult. Only few studies have been carried out in patients (Bromm and Treede, 1991; Lankers et al., 1991; Granot et al., 2001).

Recommendation
The LEPs are the easiest and most reliable neurophysiological method of assessing function of nociceptive pathways; in clinical practice their main limit is that they are currently available in too few centres. Late LEPs (which assess A-delta pathways) are diagnostically useful in peripheral and central neuropathic pains (grade B recommendation). The experience as a tool for assessing treatments is so far insufficient. More studies on ultralate LEPs in patients with neuropathic pain are encouraged.

Functional neuroimaging
Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure with different methods cerebral blood flow (rCBF) or metabolic changes that reflect local synaptic activity in defined brain regions. ‘Activation’ studies investigate changes specifically associated with a given task or a particular stimulus by comparing statistically ‘activated’ and ‘control’ conditions.

In experimental pain, fMRI and PET studies have disclosed a network of brain regions that are activated by noxious stimuli. These regions constantly include the secondary somatosensory cortex (SII), the insular cortex, the anterior cingulate cortex (ACC), and with slightly less consistency the contralateral thalamus and primary somatosensory cortex (SI) (Peyron et al., 2000). Activation of the lateral thalamus, SII and insula are thought to be related to the sensory–discriminative aspects of pain processing, while ACC, and also the posterior parietal and prefrontal cortices, appear to participate in the affective and attentional concomitants of pain sensation, as well as in response selection.

In patients with chronic spontaneous neuropathic pain, there is converging evidence from several independent groups (but for a total of 41 patients only) that unilateral pain is associated with decreased resting rCBF in contralateral thalamus, and that such rCBF decrease can be reverted by analgesic procedures (class III: Hsieh et al., 1995; Iadarola et al., 1995; Garcia-Larrea et al., 1999). This suggests that thalamic hypoperfusion contralateral to pain might be used in the future as a marker of neuropathic pain, and that restoration of thalamic blood flow could be used to monitor treatment. Although analgesic procedures including opiates and neurostimulation have induced rCBF increase in ACC, the number of patients tested is still too small to decide whether this can be a marker of
efficacy. In patients with provoked neuropathic pain, allodynia and hyperalgesia have been associated with amplification of the thalamic, insular, SI and SII responses, but not ACC (class III: Iadarola et al. 1995; Baron et al. 1999). Again the number of examined patients is still too small (Peyron et al., 2000). We encourage imaging studies in patients with allodynia.

The combination of administration of drugs with fMRI in order to elucidate pharmacological effects on brain function (pharmacological fMRI) has been recently proposed. The assessment of the effect of analgesic drugs on pain-related brain activity would provide a better understanding of pain and analgesia and hence the development of novel therapeutic strategies. However, data in patients are still lacking.

Recommendation
There is converging evidence that chronic spontaneous neuropathic pain is associated with decreased activity in contralateral thalamus, whereas provoked neuropathic pain is associated with increased activity in the thalamic, insular and somatosensory regions (grade B statement).

In view of the potential relevance of these data, we encourage functional neuroimaging studies in patients with neuropathic pain.

Biopsy
Painful neuropathies are characterized by preferential involvement of unmyelinated and thinly myelinated nerve fibres. Nerve biopsy may not be useful in the early detection or monitoring the progression of small fibre neuropathy as small fibres are difficult to quantify, and require the use of an electron microscope (Llewelyn et al., 1991). There is growing evidence that simple unmyelinated fibre counts in nerve biopsies fail to reflect the degree of unmyelinated fibre degeneration (class II: Hermann et al., 1999; Periquet et al., 1999). The procedure itself may cause considerable discomfort and may occasionally be associated with complications like pain, infection and permanent sensory loss. However, nerve biopsy is indicated if diagnostic considerations include amyloidosis or vasculitis.

Punch skin biopsy was suggested as an alternative approach to the assessment of small fibre involvement allowing the quantification of C fibres and Aδ nerve fibres through the measure of the density of intra-epidermal nerve fibres (IENF). The loss of IENF was demonstrated in a variety of neuropathies including small fibre sensory neuropathies (class II: McCarthy et al., 1995; Holland et al., 1997, 1998). Skin biopsy has recently been proved able to investigate mechanoreceptors and their myelinated afferents (Nolano et al., 2003). Punch skin biopsy is easy to perform, is minimally invasive, and most suitable for follow-up. However, it is currently available in only few research centres.

Recommendation
Often a cause for underlying neuropathy may not be found despite extensive investigations, and careful evaluation is needed before such cases are considered as idiopathic or ‘psychogenic’. Punch skin biopsy, which can detect changes when sural nerve biopsy is still normal, is emerging as a minimally invasive tool for detecting small fibre involvement; in pain patients it should be preferred to nerve biopsy (grade B recommendation).

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References


Hunt SM, McKenna SP, McGwen J, Backett EM, Williams J, Papp E (1980). A quantitative approach to perceived health...
Sjolund KF, Belfrage M, Karlsten R et al. (2001). Systemic adenosine infusion reduces the area of tactile allodynia in

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### Previous guidelines or recommendations

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