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REVIEW

# Refined sensory measures of neural repair in human spinal cord injury: bridging preclinical findings to clinical value

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**Abstract** Sensory input from the periphery to the brain can be severely compromised or completely abolished after an injury to the spinal cord. Evidence from animal models suggests that endogenous repair processes in the spinal cord mediate extensive sprouting and that this might be further attenuated by targeted therapeutic interventions. However, the extent to which sprouting can contribute to spontaneous recovery after human spinal cord injury (SCI) remains largely unknown, in part because few measurement tools are available in order to non-invasively detect subtle changes in neurophysiology. The proposed application of segmental sensory evoked potentials (e.g., dermatomal contact heat evoked potentials and somatosensory evoked potentials) to assess conduction in ascending pathways (i.e., spinothalamic and dorsal column, respectively) differs from conventional approaches in that individual spinal segments adjacent to the level of lesion are examined. The adoption of these approaches into clinical research might provide improved resolution for measuring changes in sensory impairments and might determine the extent by which spontaneous recovery after SCI is mediated by similar endogenous repair mechanisms in humans as in animal models.

**Keywords** Spinal cord injury · Segmental sensory assessment · Neural repair · Somatosensory evoked potentials · Contact heat evoked potentials

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**Abbreviations**

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| AIS | ASIA impairment scale |
| ASIA | American Spinal Injury Association |
| dCHEPs | Dermatomal contact heat evoked potentials |
| dSSEPs | Dermatomal somatosensory evoked potentials |
| EPT | Electrical perception threshold |
| QST | Quantitative sensory testing |
| SCI | Spinal cord injury |
| TRP | Transient receptor potential |

## Introduction

Basic science research in neural repair and regeneration has revealed profound insights into a variety of potential therapeutic targets that might ameliorate the neurological consequences of spinal cord injury (SCI) at some point in the future (Bradbury and McMahon 2006). Whereas the underlying changes in neuroanatomy and physiology can be readily disclosed during the course of a preclinical study, the translation of these findings into clinical trials involving humans is still fraught with limitations. In particular, the translation of potential novel therapeutic strategies from "bench to bedside" in order to treat SCI is challenged by a lack of sensitive and valid outcome measures to detect a clinically meaningful change (Steeves et al. 2007). Fundamentally, the outcomes employed as endpoints to assess efficacy in clinical trials should be sufficiently sensitive to reveal changes within the nervous system, while being related to a clinically important difference. However, the focus initially should be on devising methods that can measure even extremely subtle changes in animal models, thus confirming the existence of similar recovery mechanisms in humans. This would represent an important first step in bridging the gap between preclinical and clinical research.

Sensory deficits are among the most challenging of neurological consequences to describe after SCI. In the case of these deficits, neither the underlying changes in neuronal function nor the affective component can be readily translated from the animal model to the human experience. Comparatively, motor deficits can be observed in both preclinical animal and clinical human studies. In the interest of improving our understanding of sensory function in human SCI, novel sensory assessments have been developed that target changes occurring within individual spinal segments near the level of SCI and that are specifically designed to assess the damage in distinct sensory pathways.

## Translational research

In order to enhance the translation of preclinical findings to humans with SCI, the International Campaign for a Cure of SCI Paralysis (or the ICCP) have developed guidelines for the conduction of forthcoming clinical trials (Stevees et al. 2007). Additionally, the European Multicenter Study about SCI (www.emsci.org) was initiated in 2001 in order to improve our understanding of the course and trajectory of spontaneous recovery (Curt et al. 2004). An important contribution of this database to translational research has been to improve the prediction of long-term outcomes based on acute findings (van Middendorp et al. 2011).

The anticipated effect of most early interventions applied in humans with SCI is expected to be modest. Combinatory treatments, including cell-based therapies that promote neuroprotection during the acute phase of injury and, in later phases, neural repair (i.e., enhanced sprouting), might be necessary to achieve success in pivotal clinical studies (Bradbury and McMahon 2006). Therefore, the ability to measure small changes attributable to each therapeutic (e.g. cell based therapies) included in the combination will be of the utmost importance. Additionally, spontaneous neurological and functional recovery, attributable in part to ongoing neural repair and compensation, might make it difficult to discern treatment effects (Curt et al. 2008). Thus, a study that aims to treat the neurological consequences of SCI during the acute phase (e.g., by administering a therapeutic agent in the first 72 h) must demonstrate efficacy in a treatment group compared with a control group that is also undergoing considerable recovery. Further, there remains a lack of measurement tools senstive enough to reveal subtle improvements related to changing neurophysiology (Ellaway et al. 2004, 2011). Although spinal axons might have the capacity to regenerate over short distances (in the domain of millimeters), in the context of the human spinal cord anatomy, this implies that a similar magnitude of change in man might only be detected over one or two segments adjacent to the lesion side.

We need to bear in mind that, in addition to the beneficial aspects, aberrant sprouting might also lead to detrimental rewiring, potentially resulting in unfavorable side-effects (Marcol et al. 2007; Pezet and McMahon 2006). This might include neuropathic pain and autonomic dysreflexia (Bradbury and McMahon 2006; Weaver et al. 2001).

## Recovery of sensory function after SCI

SCI is characterized by the disruption of ascending and descending spinal white matter tracts at variable lesion levels and frequently leads to chronic disability and comorbidity. The extent of sensorimotor impairment largely depends on the severity of damage in the ascending and descending pathways. Spontaneous functional recovery after SCI depends on a variety of factors, including improvements in sensory and motor function. Notably, the recovery and integration of sensory function with regards to the body state and the environment (i.e., proprioception) is crucial for the recovery of motor function (Frigon and Rossignol 2006). Evidence from animal models suggests that extensive sprouting of afferent fibers occurs spontaneously and can be enhanced by specific therapeutic interventions (Blesch and Tuszynski 2009). However, the translation from bench to bedside remains challenging and no current standard treatments are available for SCI. In comparison with animal models, the demonstration of sprouting in humans can only be measured indirectly by the employment of non-invasive measurement techniques. The non-invasive assessment of sensory function in animal models is generally limited to observations of a behavioral response to a stimulus. These include hot-plate and cold sensitivity tests, von Frey filaments, the withdrawal reflex and the paw compression test (Šedý et al. 2008). The motor paralysis incurred during the course of injuring the spinal cord probably also confounds the accurate assessment of sensory deficits in animals. The drawback of electrophysiological and functional magnetic resonance imaging, which can also be performed in humans, is that these measurements need to be performed in anesthetized animals and hence the cognitive and attentive component is lost (Beydoun et al. 1993). In conjunction with objective measurements of sensory impairment, ratings of perceived intensity and threshold measurements can be assessed in response to standardized stimulus in humans.

## Assessment of sensory function in human SCI

The International Standards for the Neurological Classification of SCI (ISNCSCI) has become a standard clinical tool with which to assess sensory function after SCI (Maynard et al. 1997). Light touch (i.e., epicritic sensation) and pinprick

sensation (i.e., protopathic sensation, which includes sharp-dull discrimination) are assessed in cervical, thoracic, lumbar and sacral dermatomes rostral and caudal to the level of injury (i.e., segmental approach). This detailed neurological assessment permits the spinal segmental location of any preserved sensory function (i.e., sensory level of injury), with the quality of the sensation scored by a three-point ordinal scale (normal, impaired, absent). This scale has obvious problems in terms of tracking changes in sensation, particularly in those that are impaired. Further, these measurements of sensory function have shown minor and less consistent changes attributable to spontaneous recovery in comparison with measurements of motor function, which are graded on a six-point scale (0–5, i.e., complete paralysis to normal muscle strength; Curt et al. 2008; Zariffa et al. 2011; Fig. 1). Quantitative sensory testing (QST) has been proposed in order to refine sensory measurements after SCI (Hayes et al. 2002). QST attempts objectively to measure sensory thresholds to different stimuli modalities (e.g., vibration, heat, cold and pain; Shy et al. 2003). At present, QST still needs further investigation to demonstrate responsiveness to changes in impaired sensation. The use of electrical perception threshold (EPT) has been proposed as a complement to light touch and pinprick findings in chronic SCI patients (Ellaway et al. 2011). However, a more recent systematic investigation has failed to support the earlier findings (Van Hedel et al. 2011).

Regardless of the limitations of QST with regards to responsiveness, sensory thresholds do not disclose specific insights into the mechanisms underlying changes in sensation and the readouts remain subjective based on a patient report.

## Clinical electrophysiological assessments

Neurophysiological assessments are employed in order to provide complementary and objective information regarding sensory and motor deficits after SCI based on estimates of conduction (e.g., latency) in defined ascending (i.e., dorsal columns) and descending pathways (i.e., corticospinal

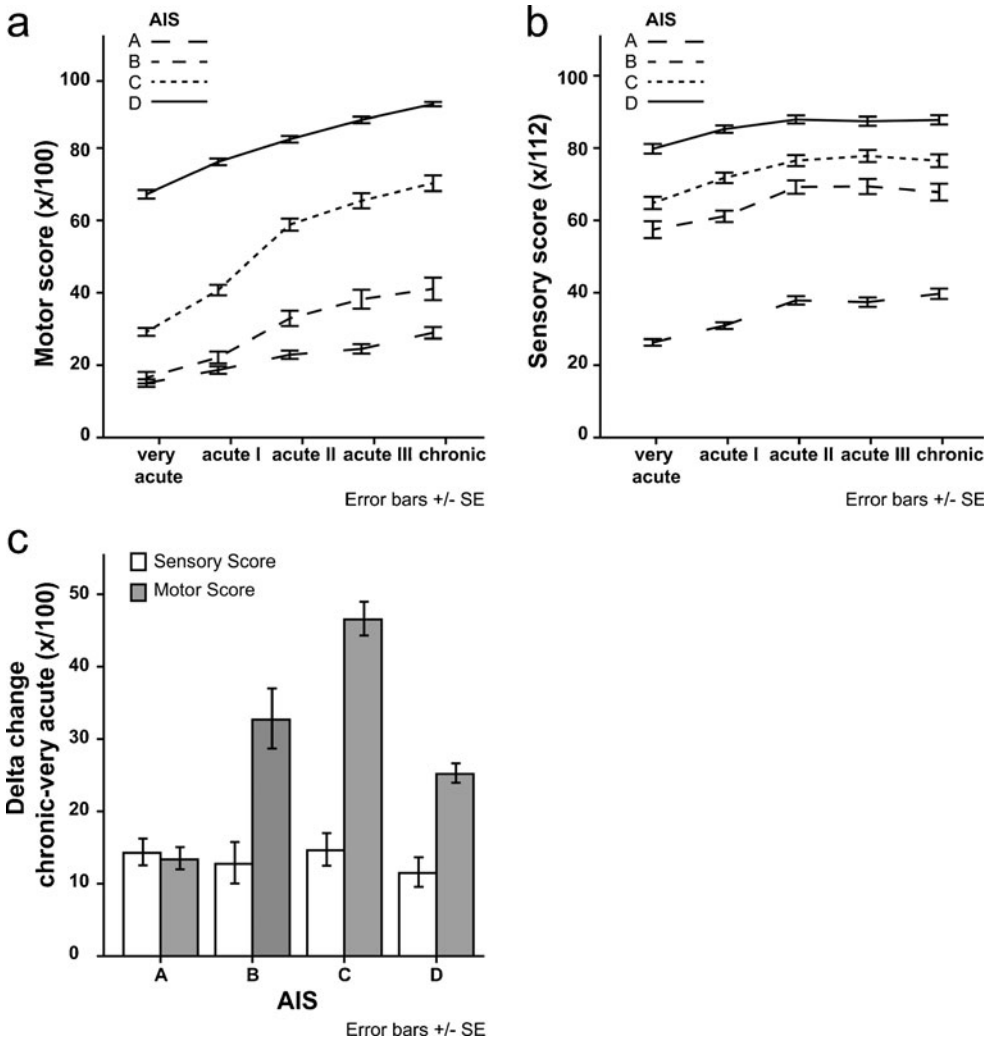


**Fig. 1** **a**, **b** Course of recovery from very acute (2 weeks post injury) to a chronic stage (48 weeks post injury) based on sensory-motor scores (American Spinal Injury Association [ASIA] motor and light touch scores) in ASIA impairment scale (*AIS*) *A-D* patients (spinal cord injury [SCI] patients from the data set of the European Multicenter Study about SCI: *AIS A* 211, *AIS B* 86, *AIS C* 114, *AIS D* 305). In comparison with the motor scores, which reveal a trend to spontaneous recovery, the recovery disclosed by the sensory light touch score is minor. **c** Delta spontaneous recovery between the chronic and the acute phase after SCI for both the sensory (ligh touch) and motor score in AIS A–D patients

tract). Generally speaking, neurophysiological approaches aim to assess longitudinal or segmental pathways (Fig. 2). Conventional somatosensory evoked potential (SSEPs) are recorded in response to electrical stimulation of mixed nerves in the periphery. Following SCI, SSEPs (e.g., tibial nerve) provide an objective measure of the severity of damage through the epicenter of the lesion. Based on these findings, the overall or "global" deficits as measured in the dorsal column are revealed. These methods have shown limited responsiveness in the detection of spontaneous recovery after SCI (Curt et al. 2004; Spiess et al. 2008). Furthermore, conventional SSEPs do not indicate the severity of disrupted ascending pathways in the more ventral spinal cord.

## Improved assessment of segmental sensory function

Whether conventional longitudinal SSEPs can also detect subtle changes in neurophysiology occurring at or near the level of SCI is not clear. This might be important for interventions that aim to improve function in adjacent spinal segments. In order to understand the extent and completeness of SCI, a segmental approach along the spinal axis is required that evaluates several dermatomes close to the area of cord damage. Dermatomal contact heat evoked potentials (dCHEPs) and dermatomal somatosensory evoked potentials (dSSEP) represent potential solutions for assessing changes in sensory function in individual spinal segments. Stimulation of thinly myelinated Aδ fibers and myelinated Aβ fibers (contact heat and electrical, respectively) allows a distinct assessment of different sensory pathways. In combination, these techniques increase the cross-sectional area of the spinal cord under investigation and thus provide a more complete picture of the damaged area (Fig. 3). For both methods, stimuli are applied to the defined sensory key points of the International Clinical Standards for Examination of Sensory Function after SCI (i.e., ISNCSCI; Alexander et al. 2009). An additional advantage of a segmental approach is that the results can be directly compared with clinical light touch and pinprick findings.

dSSEP are evoked by electrical stimulation of the dermatome to be assessed. In a recent study, dSSEPs have been employed in conjunction with EPT to assess impairments in individual cervical spinal segments (Kramer et al. 2008). In a follow-up study, dSSEPs have been shown to recover toward normal latency values during spontaneous recovery in spinal segments affected by SCI (Kramer et al. 2009b).

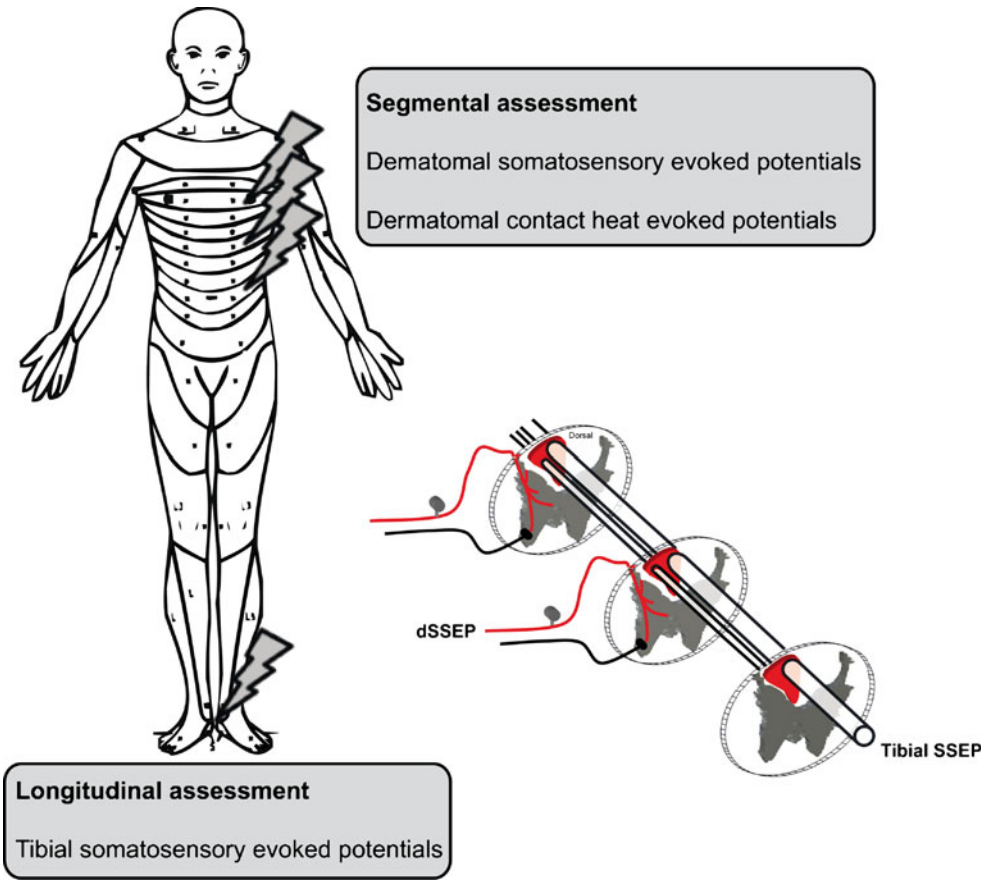


**Fig. 2** Neurophysiological measurements are commonly performed by assessing longitudinal pathways. In order to enhance the resolution to changes happening close to the level of lesion, segmental assessments with electrical (dermatomal somatosensory evoked potentials [dSSEP]) and heat (contact heat evoked potentials) stimulation can be applied to dermatomes adjacent to the lesion side (*flashes* indicate where the stimuli are applied). In the segmental assessment, thoracic dermatomes are indicated for display purposes; however, cervical dermatomes can also be assessed. The representation of the spinal cord compares tibial SSEP with dSSEP. dSSEP in SCI are assumed to be more sensitive to the level of lesion and damage to the dorsal horn and central gray area of the cord than tibial SSEP

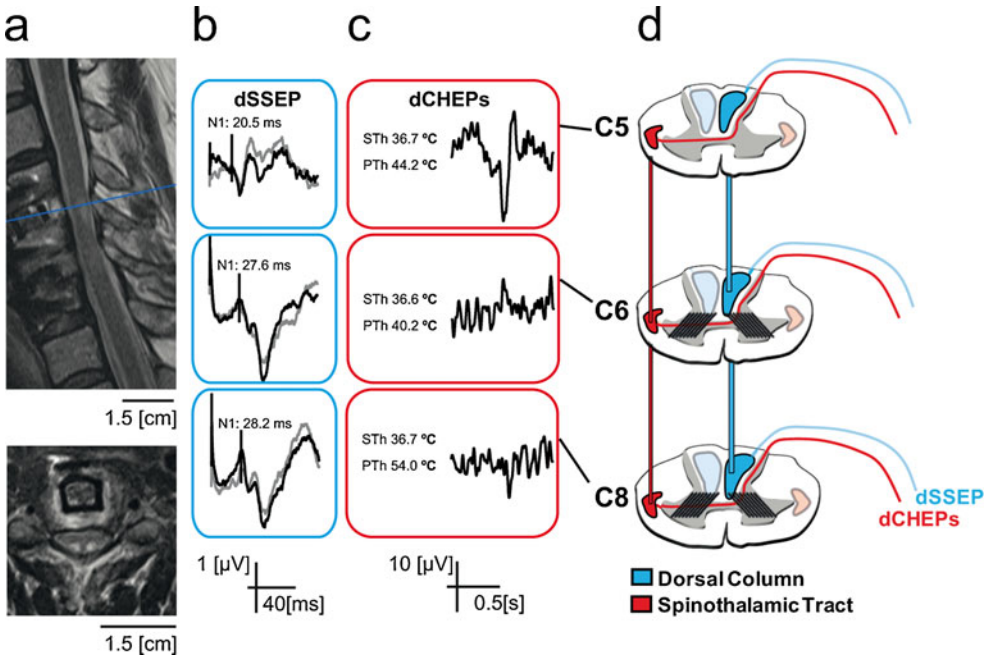


**Fig. 3** **a–c** Structural magnetic resonance imaging (MRI; **a**) of a patient example (incomplete tetraplegia, AIS D, snake-eye syndrome) with the corresponding dermatomal somatosensory evoked potentials (dSSEP; **b**) and dermatomal contact heat evoked potentials (dCHEP; **c**) showing sensory threshold (*STh*) and pain threshold (*PTh*). For the dSSEP, two consecutive runs are displayed in *gray* (first run) and *black* (second run). **d** Distinct location of the dorsal column from the spinothalamic tract in a representation of the spinal cord with the affected regions indicated by *shading*. This example clearly shows that dSSEP can assess an anatomically distinct part of the spinal cord compared with dCHEP. Whereas dSSEP values are in a normal range, dCHEPs show clear impaired and abolished evoked responses in *C6* and *C8*. Threshold measurements lack the sensitivity to display this impairment

dCHEPs have a demonstrated value for assessing the integrity of conduction in the spinothalamic tract and alternations of thermal sensitivity (Chen et al. 2001; Wydenkeller et al. 2008). Contact heat as a noxious stimulus induces depolarization at nociceptive free nerve endings of Aδ fibers and C fibers. Unlike radiant heat stimulation (i.e., lasers), which have also been employed to investigate conduction in the spinothalamic tract (Cruccu et al. 2000), contact heat indirectly activates low threshold mechanosensitive Aβ fibers via pressure applied to the skin surface. Although Aδ, C and Aβ fibers can all be activated by contact heat, the resulting evoked potentials are primarily considered to be a reflection of Aδ fibers (Mouraux and Plaghki 2007). Transient receptor potential (TRP) ion channels located on primary afferent neurons play a crucial role in cutaneous thermal sensation. TRP ion channels can be activated by distinct temperature ranges (Schepers and Ringkamp 2009; Willis 2009). TRP vanilloid 1 and 2 are transducers of noxious heat and are activated by temperatures equal to or higher than 42°C and 52°C, respectively (Willis 2009). The action potentials generated in the periphery ascend from the peripheral tissue nociceptors and enter the spinal cord via the dorsal root. Aδ fibers project primarily to laminae I and V in the dorsal horn, whereas C fibers terminate in laminae I and II (Craig 2003; Zeilhofer 2005). The primary projections of Aδ fibers decussate on the segmental level by the central gray matter and project to the spinothalamic tract of the contralateral side. A proportion of these fibers also ascends in the tract of Lissaeur, one to two segments before decussating in adjacent segments and ascending in the spinothalamic tract (Denny-Brown et al. 1973). Since lesions often affect the central gray matter (McDonald and Sadowsky 2002), dCHEPs might be more likely to indicate spinal cord pathology in a dermatomal approach compared with dSSEPs.

dSSEP and dCHEPs can give further and distinct information about spinal cord pathology. dSSEP have the advantage of occurring as a highly synchronized afferent volley, because of conduction along the fast-conducting Aβ fibers. However, the dermatomal map of small diameter fibers has been proposed to be less overlapping than that of larger diameter fibers and thus, dCHEPs might be better suited to investigating individual segments (Lee et al. 2008). Furthermore, the decussation of Aδ fibers within the segment or adjacent segments results in higher resolution for detecting spinal cord pathology compared with dSSEPs, which are limited to only the posterior spinal cord. Even though evidence exists that sensory segmental assessments are responsive enough to detect recovery, this needs to be verified in a longitudinal study in acute SCI subjects (Kramer et al. 2009a).

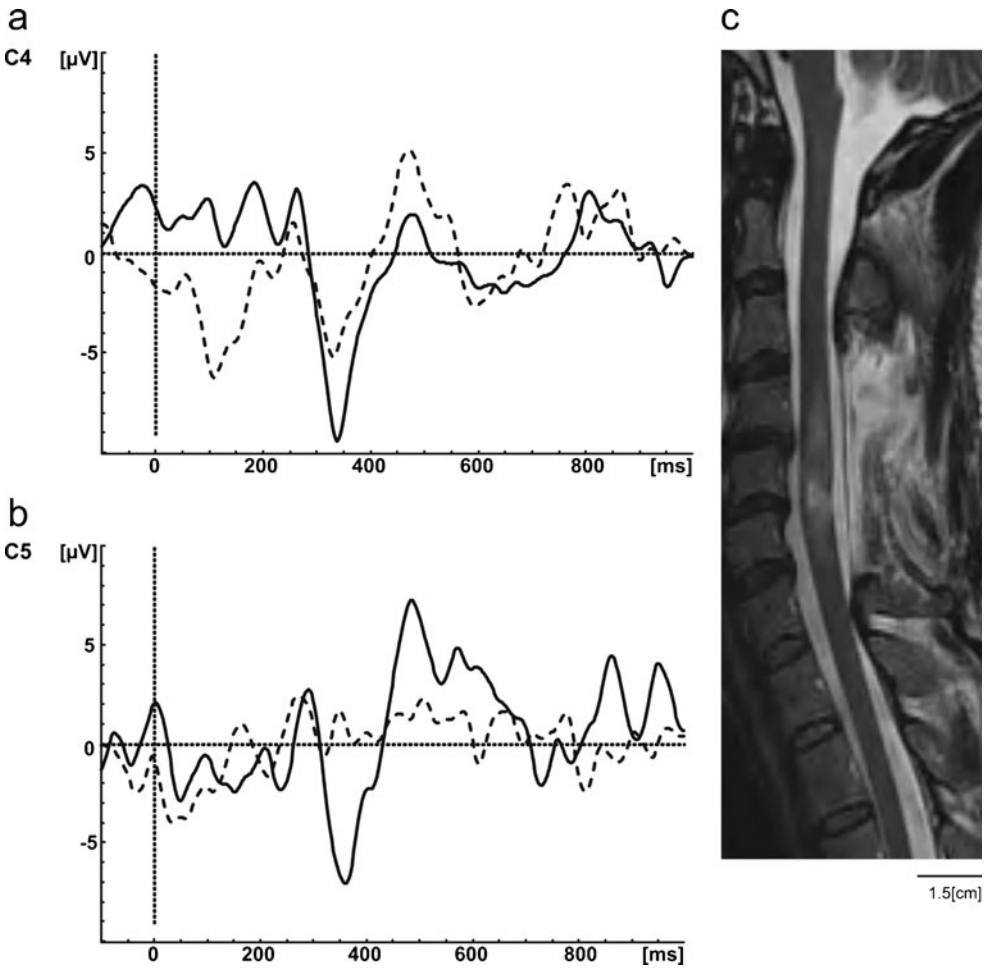


**Fig. 4** Conditioning stimulation of contact heat evoked potentials (dCHEPs) by electrical Aβ fiber stimulation (intensity below 3 mA) revealed (**b**) inhibitory effects at the dermatome C5 that clinically presented an allodynic pain syndrome. **a** No obvious effect at C4 segment above the injury level with normal sensation (*dotted line* conditioning stimulation, i.e., electrical and contact heat stimulation, *continuous line* contact heat stimulation). **c** Corresponding structural MRI of the patient (recordings of a 53-year-old male subject with traumatic SCI C4 AIS C)

In addition to reduced or completely lost sensation, SCI might result in complex sensory problems, including spontaneous neuropathic pain, allodynia and paraesthesia. The underlying neurophysiological basis of these sensory complications has not yet been thoroughly characterized. Preservation of some spinothalamic tract function seems to play a crucial part in the development of central pain after SCI (Finnerup et al. 2007; Wasner et al. 2008), although this has largely only been confirmed by using QST approaches. In order to define the sensory deficits more precisely and to improve our understanding of its relationship to sensory complications, novel stimulation paradigms may have to be designed. For example, sensori-sensory interaction between Aβ fibers and Aδ fibers might demonstrate sprouting in the dorsal horn area of the cord after SCI. This could be achieved by concomitant segmental electric and thermal stimulation being applied to the same dermatome while recording evoked potentials (Fig. 4). Kupers et al. (2011) have shown, in a small number of subjects, that laser evoked potentials in neuropathic pain patients are modulated by concomitant peripheral nerve stimulation. The conditioning of Aβ fibers during dCHEPs might provide a test to estimate and quantify the sensori-sensory interaction and might serve as a mean to disclose sensory complications at the level of lesion in SCI subjects.

## Concluding remarks

To date, sensitive measurement methods to assess changes close to the level of SCI are clearly lacking. A more detailed assessment of segmental sensory deficits by adopting segmental neurophysiological approaches might improve clinical trial protocols by addressing the limitations of clinical sensory testing, which has failed to be sufficiently sensitive and responsive for these purposes. dSSEP and dCHEP might serve as complementary assessment tools to detect changes attributable to spontaneous recovery and further serve as important outcome measurements to detect the efficacy of therapeutic interventions.

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