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Methods to measure sensory function in humans versus animals

Alberto Martinez-Arizala, MD
Veterans Affairs Rehabilitation Research and Development Center of Excellence in Functional Recovery in Chronic Spinal Cord Injury, Veterans Affairs Medical Center, Miami, FL; The Miami Project to Cure Paralysis, Departments of Neurology and Neurosurgery, University of Miami School of Medicine, Miami, FL

Abstract—Sensation is perhaps one of the most complex senses. It allows us to experience our environment, and it provides ongoing feedback for the performance of accurate motor tasks. The present methods used for clinical testing of sensation in patients with spinal cord injury (SCI) rely on traditional techniques developed many years ago. This type of testing has been incorporated into the ASIA (American Spinal Injury Association) score, which has become the principal instrument for measuring the recovery of sensory function in humans. Unfortunately, the ASIA score lacks sophistication and is not quantitative. Similar shortcomings are found in the testing of sensation in experimental animal models of SCI. Although highly refined methods have been developed for the study of sensation and pain perception in animals, these methods have not been incorporated for measuring recovery of function in experimental SCI. A review of the available literature suggests that further refined and quantifiable tests need to be developed in this area.

Key words: current perception thresholds, quantitative sensory testing, sensory systems, spinal cord injury, thermal somatosensory testing.

INTRODUCTION

The integration and processing of the different, complex somatic sensory stimuli provides numerous critical functions in our daily lives. First and foremost, it allows us to experience and navigate through our environment. The somatic sensory modalities include touch, proprioception, pain, and temperature (for a review, see Gardner and Martin [1]). Normal sensation permits us to enjoy pleasurable sensations and warns us of potential or actual tissue damage. Equally important is the proprioceptive component, which provides us the ability to perform coordinated motor tasks that would be difficult without proper sensory-motor integration.

Although the loss of motor function has become the main concern following spinal cord injury (SCI), SCI also produces profound dysfunction of sensory and autonomic pathways. The loss of normal sensory function has significant effects on the daily lives of patients with SCI. In addition, sensation is unique among the senses in its response to injury. Lesions of the sensor pathways produce functional deficits (numbness), but they can also produce chronic neuropathic pain, which often can be severe [2,3].

Abbreviations: ASIA = American Spinal Injury Association, CPT = current perception thresholds, MRI = magnetic resonance imaging, QST = quantitative sensory testing, SCI = spinal cord injury.

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Address all correspondence and requests for reprints to Alberto Martinez-Arizala, MD; Miami Veterans Affairs Medical Center, Spinal Cord Service, 1201 NW 16th Street, Miami, FL 33125; 305-575-3124; fax: 305-575-3161; email: amartinez@miami.edu.

RATIONALE FOR MEASURING SENSATION IN SPINAL CORD INJURY

Testing sensory function after SCI allows us to measure the degree of dysfunction and the degree of recovery. As new therapies for the treatment of SCI arise, it is important to have adequate tests that accurately measure sensory function in both animals and humans. One of the biggest hurdles is that testing of sensory function in humans, particularly pain, remains largely subjective. Difficulties arise in choosing appropriate tests for the different sensory modalities and in the interpretation of those test results. For example, tests may detect a statistically significant *p* value, but it may have little or no clinical significance.

Whether in animal or human trials, another issue to consider is the feasibility of the tests used to measure sensory function. The tests have to be reproducible across different examiners and administered in a time-efficient manner. Such tests have already been developed to determine the recovery of motor function following SCI in animals [4]. Although this testing was developed for locomotor function, in reality it tests sensory-motor integration, since it grades the walking ability of a rat. Our goal should be to develop and use tests that will allow us to predict clinically relevant recovery of sensory function more accurately. Recovery of sensory function could manifest improvement in such areas as (1) skin care (prevention of decubiti); (2) bowel, bladder, and sexual function; (3) the performance of coordinated motor tasks; and, ultimately, (4) independence in self-care and the activities of daily living. Additionally, the development of sensory tests that could help predict those SCI patients at risk for experiencing neuropathic pain would be extremely useful.

SENSORY MODALITIES TESTED IN HUMANS

The primary modalities that can be easily tested at the bedside include touch, pain, temperature, vibration, and position sense. Tests used today became part of the standard neurological exam procedure in the late 19th century (for a detailed review, see Cassiopeia and Okun [5]). At that point, the association of pain and temperature in a common pathway, the existence of a crossed afferent tract, and the dissociation of pain/temperature and position senses had been appreciated [5]. Little has changed in the manner of testing today. However, for measuring sensory function in SCI, the exam has focused on light touch and pinprick, as recorded in the ASIA (American Spinal Injury Association) score and as delineated in the International Standards for Neurological Classification of SCI (last revised in 2002). This has been the tool used in the last two large human SCI cooperative trials, where methylprednisolone was reported to be beneficial [6,7].

The present ASIA sensory score has significant limitations. First, the manner in which sensory function is assessed remains imperfect. Sensory scores for each dermatome are assigned as 0 = absent, 1 = abnormal, and 2 = normal. With this coding system, patients who perceive a pinprick as minimally sharp touch are assigned the same score as those who perceive it as almost normal. A similar situation exists in the grading of light touch. The ability to glean minor grades in recovery is lost with this assessment tool. Second, the grading of posterior column function is ignored in this system. The simple addition of testing vibration or position sense would not suffice, as recent studies suggest that this information is also carried through the anterolateral pathways of the spinal cord [8].

Lastly, a variety of sensory tests that require cortical integration (stereognosis, graphesthesia) are available, but their usefulness to assess the recovery of sensory function is unknown. Some of these tests are impractical to administer to an SCI patient, since paralysis can interfere with the performance in these tests. For example, stereognosis testing in a tetraplegic with significant hand weakness would be difficult, if not impossible.

SENSORY MODALITIES TESTED IN ANIMALS

A significant number of tests have been developed to assess sensory function in animals. Unfortunately, present experimental SCI studies focus on measuring motor recovery or improvements in physiological or neurochemical processes [9], and sensory function is neglected. A number of sensory tests in animal models have been used to determine the physiology of sensation and pain, but these tests have not been applied to measure recovery of function in experimental SCI. It is notable that most studies aimed at developing treatments in experimental SCI use the rat as the preferred animal model. Tests used to assess sensory function in rodents measure animal responses and/or reaction time to various stimuli. Examples of this include (a) devices that measure

the animal's response to heat applied to its paw (hot plate) and (b) devices that measure the animal's response to mechanical pressure (paw pinch or von Frey hair testing). Elaborate electronic models of these testing devices have been developed, and they are described in more detail by Eaton in another article in this issue.*

The present tools used for sensation testing in animals also have significant limitations. First, the response time in an SCI animal may be delayed secondary to motor paralysis and not from sensory dysfunction. It may also be extremely difficult to differentiate between these two components in some animals. Second, most of these devices are more likely measuring pain instead of sensation thresholds. Third, it is difficult to account for the components of central modulation (arousal, attention, expectation, and learning) in animals. Other tests, such as neurophysiological recordings, are more accurate, but they are more time consuming and difficult to perform on a large number of animals. More refined tests of sensory discrimination have been developed for use in higher primates, but these are also increasingly tedious, time consuming, and expensive, and they can only be conducted in small numbers of animals [10–12].

OTHER METHODS OF SENSORY TESTING IN HUMANS

Our battery of sensory tests for the human SCI can be initially improved with some minor modifications to the present ASIA score. For example, the incorporation of an additional grade of function to the pinprick score might yield additional evidence of recovery of function in future studies. Given the nature of light touch testing, a similar change cannot be instituted. In addition, tests of dorsal column function could be considered for inclusion. As mentioned before, simply testing vibration or position may not accurately reflect dorsal column function. The spinal cord exhibits significant parallel processing of sensory information, and these two modalities are not subserved exclusively by the dorsal columns [8,13]. Lesion studies in primates support this and suggest that the best test of dorsal column function is having the patient determine the direction of lines drawn on the skin [12,14,15].

More refined methods have been developed for sensory assessment, but they have yet to be adapted to the point where they can be applied successfully to SCI in a large number of patients. Quantitative sensory testing (QST) is one of these methods. This technique was first described clinically by Fruhstrofer et al. in 1976 [16] and has been used primarily to evaluate peripheral nerve disorders [17,18]. While nerve conduction velocity testing measures large nerve fiber function, QST yields information from the different nerve fiber populations. These include (a) the large, fast-conducting A_β fibers, which mediate sensations of touch, mild pressure, vibration, and joint position; (b) the small, myelinated A_δ fibers, which mediate cold sensation and the first components of the sensation of pain; and (c) and the small, slow-conducting C fibers, which mediate the sensation of warmth and the main component of pain [17]. The advantages of QST are that it is more objective than the clinical examination and it produces quantifiable responses.

Presently, two types of devices are being used for QST. The most commonly used method is thermal somatosensory and vibration sensory threshold testing [17–19]. This type of device measures sensory and pain thresholds to cold and hot stimuli, as well as vibration threshold to vibratory stimuli. The data collected allow the investigator to infer nerve fiber population function. The second type of device uses current perception threshold (CPT) levels. This type of apparatus uses electrical stimuli to measure the function of different types of nerve fibers [20]. It works by delivering three different constant alternating current sinusoid waveform stimuli at 2000, 250, and 5 Hz, at intensities varying from 0.01 to 9.99 mA. These different frequencies measure a response from the different subpopulations of sensory nerve fibers: at 2000 Hz, large myelinated fibers; at 250 Hz, small myelinated fibers; and at 5 Hz, small unmyelinated fibers. A drawback to this method is that it does not use a "physiological" stimulus.

QST has several disadvantages. While it is quantifiable, QST is still a subjective test that remains operator-dependent. In addition, the parameters of QST are sensitive to the different methodological aspects of the test. These parameters include the site of testing, the pressure applied to the stimulator, the stimulator size, and subject training. The inference that can be made from results obtained by these methods to measure sensory dysfunction is not as clear in central nervous system disorders as it is in peripheral nerve disorders. An example is testing

*See Eaton M, Common animal models for spasticity and pain, this issue.

of vibration thresholds, which do not strictly reflect dorsal column function [8,13]. An additional hurdle to applying QST in the SCI population is that the test can be time consuming if many dermatomes are tested. And if selected dermatomes are to be tested, then what criteria will be used to select them? Nevertheless, sensory dysfunction studies in SCI that use QST methods are starting to surface [21–23]. It appears that these methods may be useful in the study of the central pain that occurs following SCI [23].

Functional magnetic resonance imaging (MRI) is yet another recently developed technique that can correlate sensory function with neural activity [24]. It indirectly measures neural activity by detecting changes in regional cerebral blood flow and uses this measurement as a surrogate marker for neural function. The main limitation of this method has been the limited resolution of this technique when it is applied to such small structures as the spinal cord. However, with further development, spinal cord studies are now becoming possible [25].

Experimental animal SCI studies have not included the testing of sensory function as a measure of the neurological deficit or its recovery [9]. It is understandable, since the available tests of sensory function, which record the time for limb withdrawal to a noxious stimulus, are difficult to interpret in animals whose limbs are paralyzed. However, these sensory tests may be applicable to animals with incomplete SCI. The incorporation of these tests will become important as the field of transplantation advances. If sensory testing is not incorporated, then the effects of transplants with regard to sensory function may be overlooked. These effects also include negative consequences, such as an increase in pain. It would be critical to have this type of information before transferring transplantation strategies to the human SCI.

SUMMARY

Sensory testing as a measure of functional recovery has remained relatively simple in the human SCI, and absent in animal SCI studies. The refinement of these tests for application to the human SCI and the incorporation of tests in animal SCI studies should yield additional valuable information.

REFERENCES

1. Gardner EP, Martin JH. Coding of sensory information. In: Kandell ER, Schwartz JH, editors. Principles of neural science, 4th edition. New York: McGraw Hill; 2000. p. 411–29.
2. Finnerup NB, Johannesen IL, Sindrup SH, Bach FW, Jensen TS. Pain and dysesthesia in patients with spinal cord injury: a postal survey. Spinal Cord 2001;39:256–62.
3. Widerstrom-Noga EG, Duncan R, Felipe-Cuervo E, Turk DC. Assessment of the impact of pain and impairments associated with spinal cord injuries. Arch Phys Med Rehabil 2002;83:395–404.
4. Basso DM, Beattie MS, Bresnahan JC. A sensitive and reliable locomotor rating scale for open field testing in rats. J Neurotrauma 1995;12:1–21.
5. Cassiopeia F, Okun MS. Origins of the sensory examination in neurology. Semin Neurol 2002;22:399–408.
6. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. New Eng J Med 1990;322:1405–11.
7. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. 1997 JAMA;277:1597–604.
8. Davidoff RA. The dorsal columns. Neurology 1989;39: 1377–85.
9. Martinez-Arizala A, Green BA, Bunge RP. Experimental spinal cord injury: pathophysiology and treatment. In: Rothman RH, Simeone FA, editors. The spine, 4th edition. Philadelphia: W.B. Saunders Co.; 1999. p. 1143–68.
10. Vierck CJ Jr. Alterations of spatio-tactile discrimination after lesions of primate spinal cord. Brain Res 1973;58:69–79.
11. Vierck CJ Jr. Absolute and differential sensitivities to touch stimuli after spinal cord lesions in monkeys. Brain Res 1977;134:529–39.
12. Azulay A, Schwartz AS. The role of the dorsal funiculus of the primate in tactile discrimination. Exp Neurol 1975;46: 315–32.
13. Gilman S. Joint position sense and vibration sense: anatomical organization and assessment. J Neurol Neurosurg Psychiatry 2002;73:473–7.
14. Vierck CJ Jr, Cohen RH, Cooper BY. Effects of spinal tractotomy on spatial sequence recognition in macaques. J Neurosci 1963;2:280–90.
15. Vierck CJ Jr. Tactile movement detection and discrimination following dorsal column lesions in monkeys. Exp Brain Res 1974;20:331–46.

16. Fruhstrofer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071–5.
17. Zaslansky R, Yarnitsky D. Clinical applications of quantitative sensory testing. J Neurol Sci 1988;153:215–38.
18. Quantitative sensory testing: a consensus report from the Peripheral Neuropathy Association. Neurology 1993;43: 1050–2.
19. Dyck PJ, Karnes JL, Gillen DA, O'Brien PC, Zimmerman I, Johnson D. Comparison of algorithms of testing for use in automated evaluation of sensation. Neurology 1990;40; 1607–13.
20. Dotson RM. Clinical neurophysiology laboratory tests to assess the nociceptive system in humans. J Clin Neurophys 1997;14:32–45.
21. Krassioukov A, Wolfe DL, Hsieh JT, Hayes KC, Durham CE. Quantitative sensory testing in patients with incomplete spinal cord injury. Arch Phys Med Rehabil 1999; 80:1258–63.
22. Hayes KC, Wolfe DL, Hsieh JT, Potter PJ, Krassioukov A. Clinical and electrophysiological correlates of quantitative sensory testing in patients with incomplete spinal cord injury. Arch Phys Med Rehabil 2002;83:1612–9.
23. Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. Brain 2003;126:57–70.
24. Haughton VM, Turski PA, Meyerand B, Wendt G, Moritz CH, Ulmer J. The clinical applications of functional MR imaging. Neuroimag Clin North Am 1999;9:285–93.
25. Stroman PW, Ryner LN. Functional MRI of motor and sensory activation in the human spinal cord. Mag Res Imaging 2001;19:27–32.