

Neurometer® Clinical and Research Update (10/2009)

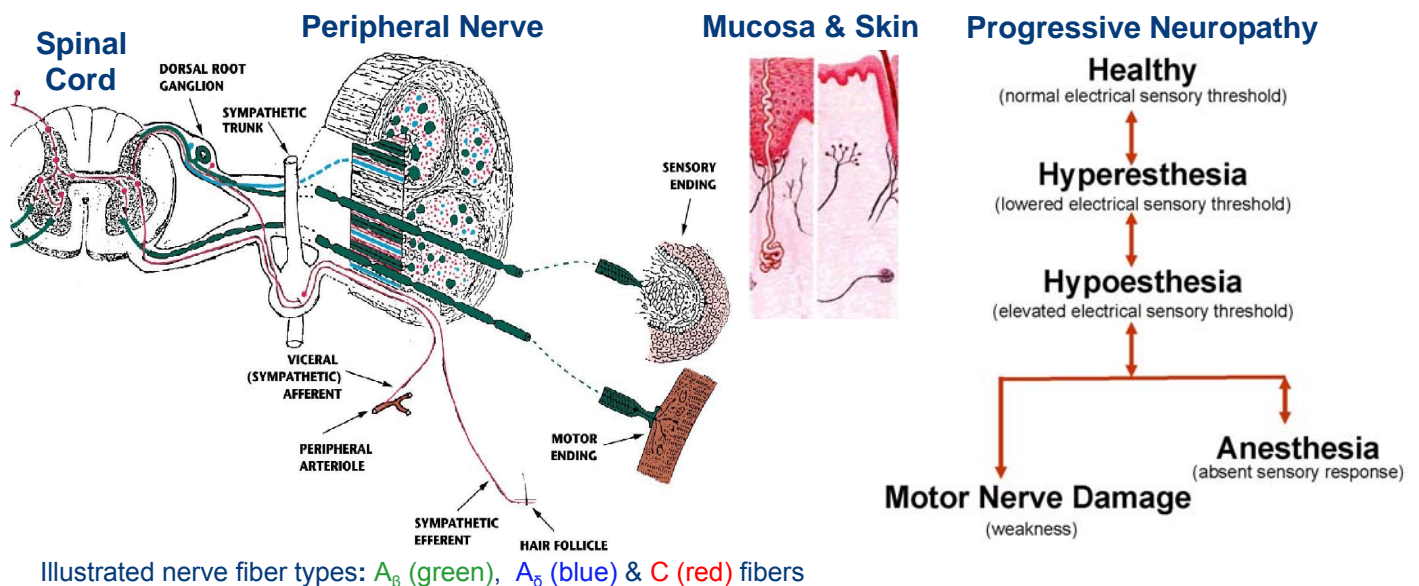
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Neurometer® Diagnostic Sensory Evaluation

More than 30 years after leaving the laboratory for clinic applications ranging from Podiatry to Neurology and dozens of other specialties in-between, the Neurometer® evaluation continues to provide unique diagnostic measures of sensory nerve conduction thresholds (sNCTs). The most widely used sNCT measure is Current Perception Threshold (CPT®) which is the minimum amount of painless electrical stimulus that consistently elicits a nerve response.

The Neurometer generates a constant current stimulus by monitoring and compensating for tissue impedance variations.¹ The stimulus evokes responses that quantify the functional integrity of each of the three major sub-populations of sensory nerve fibers. Specifically, A_β, A_δ & C fiber groups are selectively stimulated by sinusoid waveform currents of 2000 Hz, 250 Hz and 5 Hz respectively. Using small surface electrodes, this test generates discrete double-blinded CPT measures (p<0.006) representing minimum detectable current intensities (+/- 20 μAmp.) for each fiber type.²



Advantages of the Neurometer Evaluation

Common metabolic/toxic and progressive neuropathies affect sensory nerves before motor nerves. Affected sensory nerves pass through reversible stages of hyperesthesia (often sub-clinical) then hypoesthesia and anesthesia. These sensory impairments occur in specific nerve fiber sub-populations. CPT studies have the unique capacity to evaluate the full spectrum of sensory nerve function in all the major fiber sub-populations. Patients are frequently asymptomatic in the earliest stages. The earliest stage of the pathologic process is usually the easiest phase to effectively intervene. The Neurometer detects hyperesthetic sensory neuropathy in non-diabetics with impaired glucose tolerance and in non-diabetic obese individuals. This ability to detect subclinical abnormalities in conditions known to carry a high risk of polyneuropathy is a tremendous clinical diagnostic advantage. It also detects the hypoesthesia of advanced neuropathic conditions as well as nerve regeneration.³

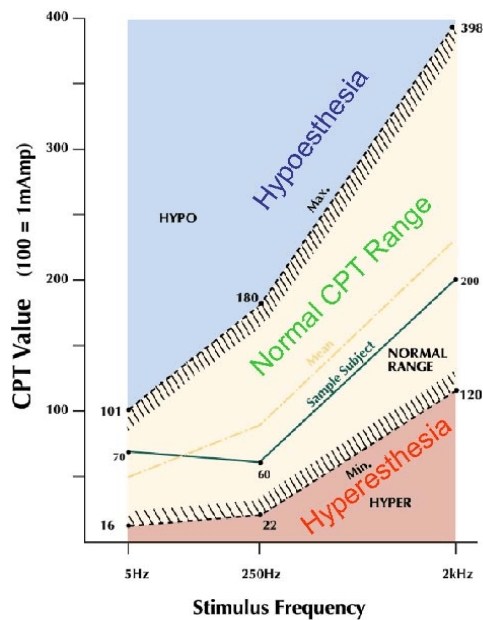
Publications confirm that sensory impairments ranging from polyneuropathies (diabetic, demyelinating, toxic) to compressive lesions (Carpal Tunnel Syndrome), radiculopathies, spinal cord lesions as well as regeneration may be neuroselectively evaluated. Additional applications of the Neurometer include pharmaceutical, cosmetic, environmental and laboratory animals.

Performing a Neurometer® Electrodiagnostic Evaluation

Painless standardized automated double-blind testing methodology is used to determine the CPT. It is based on the same psycho-physical principles used in routine hearing tests. The painless stimulus is characterized as “tingling”, “prickling”, or “buzzing”. Qualitative measures such as warm, cold, vibration, touch etc. are not a factor.

Electrodes are positioned at the prescribed test site and held in place with tape. Directions for the technician are displayed on the LCD screen. The subject is instructed to press a button until a stimulus is detected at the site of the electrode(s) and then release the button. At this point the CPT measure is verified using Compliance Guard® software. This effectively monitors responses for consistency. CPT measures are then classified by comparison to the internationally validated normative database.

Finger CPT vs. Frequency
Normal, Hyper & Hypoesthetic Ranges



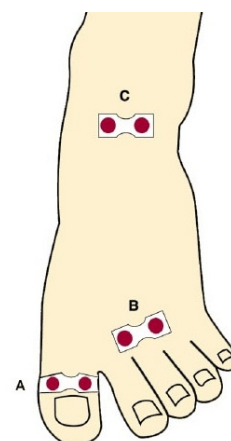
Background

Neurotron, Inc., founded in 1981, in Baltimore, MD, USA designs and develops Neurometer electrodiagnostic devices. FDA registered in 1986, the Neurometer emerged from laboratory studies at McGill University, Montreal, PQ, Canada and clinical research at the Johns Hopkins University School of Medicine, Baltimore. More than one million painless Neurometer studies have been conducted with over 600 scientific peer-reviewed publications. These affirm that this automated electrodiagnostic procedure objectively and selectively quantifies the functioning of both unmyelinated and myelinated sensory nerve fibers at any cutaneous/mucosal/dental test site. The Neurometer has been useful in guiding the clinician to choose the most appropriate therapy and for monitoring and evaluating interventions.

Polyneuropathy Diagnosis: Anatomic & Neuroselective

Mapping Polyneuropathy - Axonal vs Demyelinating

Most metabolic and toxic neuropathies typically affect sensory nerves before motor nerves and present with a dying back distribution in the tips of the toes first and later the fingers. Mapping the distribution of sensory impairment resulting from polyneuropathy and noting the type of axonal dysfunction permits the differential diagnosis of diffuse demyelinating vs distal axonal polyneuropathies.⁴ CPT measures from the big toe (A) are generally the first to be affected, ranging from the earliest hyperesthetic stage to the advanced hypoesthetic condition. Normal sensation at proximal test sites (B, C) confirms the clinical diagnosis of distal dying back polyneuropathy. In contrast, demyelinating polyneuropathies typically affect both proximal and distal CPT measures associated with myelinated fiber function (2000 Hz and 250 Hz CPTs) but not measures associated with unmyelinated fiber function (5 Hz CPTs).

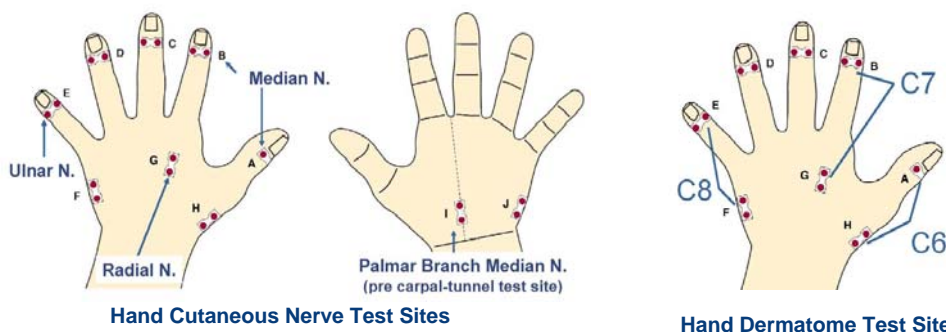


Polyneuropathy Test Sites

CPT testing at the big toe incorporates both the superficial and the deep peroneal nerves (4th and 5th lumbar dermatomes respectively, site A above). This neurological overlap prevents focal nerve lesions or mono-radiculopathies from affecting the CPT measures at this site. Conversely, symmetrical dying back polyneuropathies affecting both the superficial and deep peroneal nerves are easily detectable at this location.

Upper Extremity Differential Diagnosis

Screening for Carpal Tunnel Syndrome (CTS) is conducted at the distal phalange of the index finger (B).⁵ This site is also sensitive to vibration neuropathy (neuroselective for myelinated fibers).⁶ Guyon's canal syndrome, may be detected through a comparison of the CPT measures from a digital ulnar nerve (E) and palmar ulnar nerve (J). Upper/Lower Brachial Plexopathy is evaluated by noting the distribution of impairment.



Hand Cutaneous Nerve Test Sites

Hand Dermatome Test Sites

Carpal Tunnel Syndrome (CTS)

Early CTS is associated with hyperesthetic CPTs (abnormally low electrical excitability) reflecting inflamed nerves that have not lost their functioning. Advanced CTS, associated with a loss of median nerve function, is associated with hypoesthetic (abnormally high) CPTs. The combination of a sensory impairment detected at the distal phalange of the index finger (Site B), combined with normal CPT measures from the ulnar nerve (5th finger, Site E) and palmar branch of the median nerve (Site I), objectively confirms the clinical diagnosis of CTS. The CPT evaluation can detect CTS in the presence of a polyneuropathy. This electrodiagnostic procedure confirms the recovery of median nerve function following conservative or surgical treatment of CTS.⁵

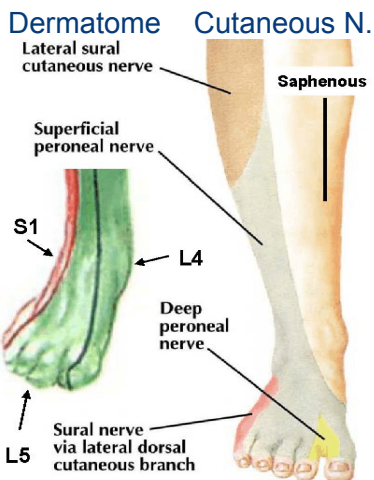
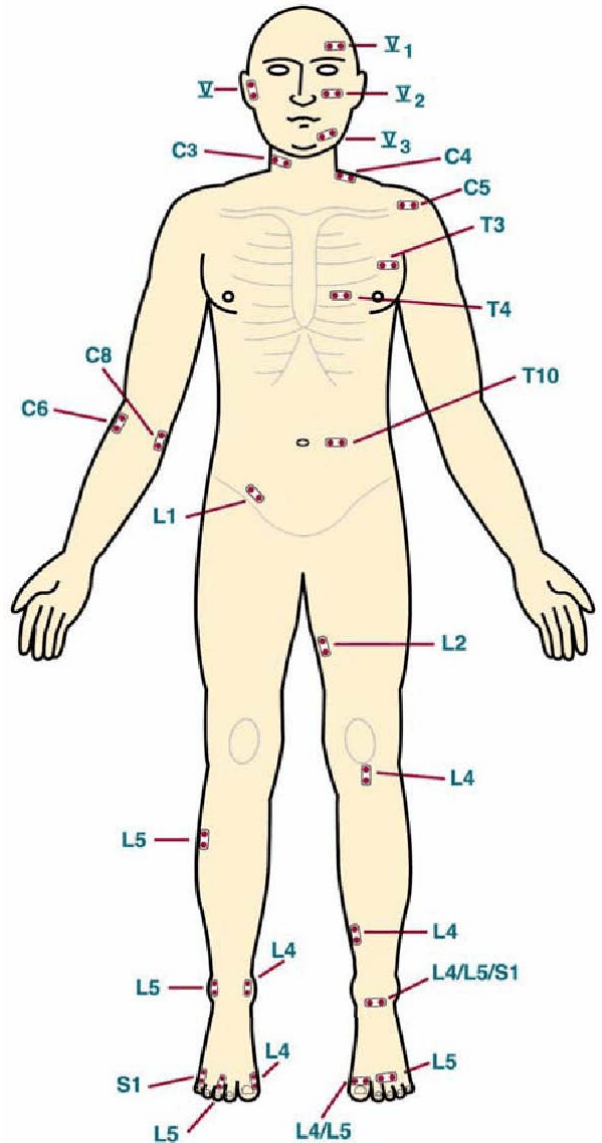
Upper Extremity Radiculopathy and Spinal Pathology⁷

CPT measures quantitate the severity of a radiculopathy. This type of diagnostic evaluation is conducted along a dermatomal distribution. Further confirmation of a radiculopathic sensory impairment would include more proximal testing in the same dermatomes. Abnormal CPT measures caused by radiculopathy, myelopathy or conditions such as syringomyelia will be confined to a dermatomal and neuroselective distribution.⁷

Lower Extremity Differential Diagnosis Radiculopathy, Myelopathy & Focal Lesions⁷

Radicular pain can mimic the pain of peripheral neuropathy, peripheral arterial disease or a focal lesion. Sensory impairments resulting from radiculopathy will affect the lower extremity along a dermatomal distribution. Testing the same dermatome at distal and proximal locations (innervated by different nerves, e.g., sites illustrated below: I- Peroneal and J- Saphenous Nerves) or the same peripheral nerve in different dermatomes (e.g., sites I-L4 and H-L5) can help confirm a suspected radiculopathy. The finding of a peripheral sensory impairments measured from several toes, combined with normal CPTs observed at proximal locations within the same dermatome suggests that the lesion involves a peripheral and not a spinal nerve. Spinal lesions or myelopathy will result in a segmental sensory impairment where all dermatomes below the level of the lesion are impaired.

CPT Dermatome Test Sites



Standardized CPT Test Sites (Norms Established)



D - (S1) Sural N.
F - (S1) Sural N.
H - (L5) Sup. Peroneal N.
J - (L4) Saphenous N.

E - (L5) Sup. Peroneal N.
G - (S1) Sural N.
I - (L4) Sup. Peroneal N.
K - (L4/S2) Tibial N.

Herniated Disc

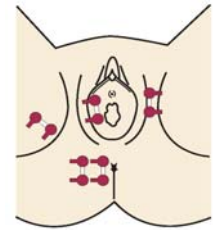
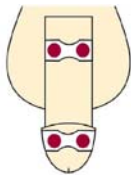


Dental, Mucosal & Genital CPT Measures

Dental testing includes tooth measures and oral mucosal measures.⁸ Neurometer measures have proved useful for uro-gyn and pharmaceutical studies as well as for differential diagnostic applications.⁹ Experimental catheter electrodes for oral, urethral (proximal and mid) and , bladder, vaginal/anal applications and other specialized electrodes are available for research.



Urethral & Bladder Catheter Electrode with Lumen (12 Fr) (positioning balloon inflated, electrode is black)



Bladdertrode™



Urotrode™ (cuff balloon)



Vaginal/Rectal G-Trode™



Neurometer® Device Threshold Test Modes

Test results are evaluated using the Neuval® Windows® software. The reports include a grading of the functional integrity for the specific nerves and their sub-fiber groups and a summary. The findings are based upon range, within-site and between-sites ratio analyses through comparison to a database of clinically established normative values. Neurometer test modes include:

Current Perception Threshold (CPT) ($p < 0.006$, resolution $\pm 20 \mu A$) - Painless Current Perception Threshold. Standardized automated double-blind determination mode requires 5-8 minutes per nerve/site.

Ranged Current Perception Threshold (R-CPT) ($p < 0.05$, Ranged CPT) - This mode allows neuroselective sensory threshold determination in approximately 2-3 minutes per nerve/site. Normative data is pre-programmed for 35 of the most common testing sites and a print out of the results immediately indicates if the subject's measures are within these norms, hyperesthetic or hypoesthetic.

Pain Tolerance Threshold (PTT) The noninvasive atraumatic PTT mode permits the neuroselective evaluation of pain. There are established PTT values for the finger and toe.

Percentile Allodynia Testing This mode provides an automated PTT test completion based on normative PTT values established for the fingers and toes enables a less painful method to evaluate allodynia than the standardized PTT evaluation.

Remote Computer & Auditory Control Windows® software is available for research and laboratory applications.

Animal Response Testing A non-invasive and harmless test permitting serial measures from the same site. The test may be used to assess any cutaneous or mucosal site using specialized electrodes for large or small animals.¹⁰ Evaluation of the concha of the ear gives direct access to brain stem neurons for CNS measures. Rat bladder electrodes are available.



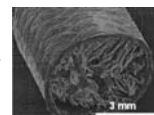
fMRI Testing Established utility for applications with fMRI technology.²⁸ Custom fMRI electrode cables are available from Neurotron, Inc. Additionally, a fMRI computer interface is available.

Other Applications



Cosmetic The application of the Neurometer in cosmetics came from dentistry and dermatology studies of sensitive teeth/oral mucosa and skin. Additionally the evaluation of the itch response has proved a useful measure.¹

Synthetic Nerves, Stem Cells and Nerve Regeneration Neurometer measures have assisted in monitoring the recovery of sensation following various implants and transplants.³



Environmental/Occupational Monitoring rice paddy farmers for pesticide and fire fighters for PCB exposure as well as detecting the toxicity from arsenic, lead, other heavy metals and vibration exposure - the Neurometer has played a key role in environmental medicine.^{11,22}



Sports Medicine Providing objective measures of sensory function of marathon runners on mountain tops and bicyclers in laboratories is made possible because of the Neurometer's portability. The battery powered Neurometer is versatile!¹²



Medical Legal Neurometer evaluations have been recognized by courts in the USA and other countries for disability evaluation.¹³

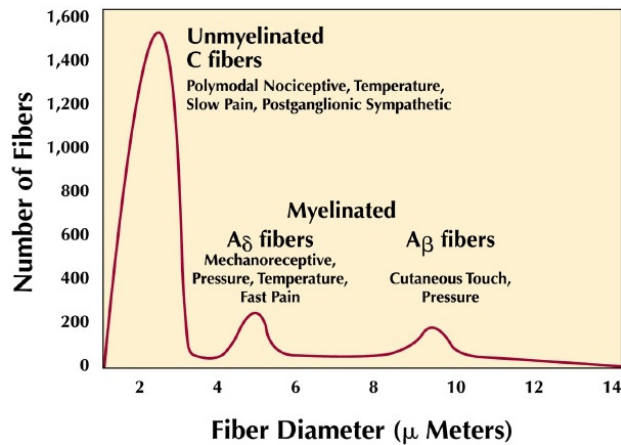
Neurometer® Technology Comparison to Other Diagnostic Procedures

Capabilities and Features	Sensory Diagnostic Study					
	CPT	SSEP	sNCV	Vib	Therm	Biopsy
Neuroselective Evaluation of All Major Sensory Fiber Types	✓					✓
Evaluate Hyperesthesia and Hypoesthesia	✓					
Test Any Cutaneous/Mucosal Site	✓					
Localize Abnormal Sensory Function from Periphery to Spinal Cord	✓	✓				
Evaluate Early and Advanced Regeneration	✓					
Detects Malingering	✓	✓	✓			✓
Unaffected by Skin Thickness, Scar Formation or Edema and Skin Temperature	✓					
Painless Measure	✓			✓	✓	
Standardized Automated double blind study	✓					

"While early intervention and treatment can be critical to slowing the disease's progression, most Americans don't recognize neuropathy's symptoms, which include weakness, numbness, tingling and pain, especially in the hands and feet. If ignored, the symptoms can intensify to loss of sensation to unremitting pain. Neuropathy may be the most common disease in the United States that you've never heard of. Many are even unaware that they have it".

Neuropathy Association, May 2008

Typical Sensory Nerve Fiber Subpopulations



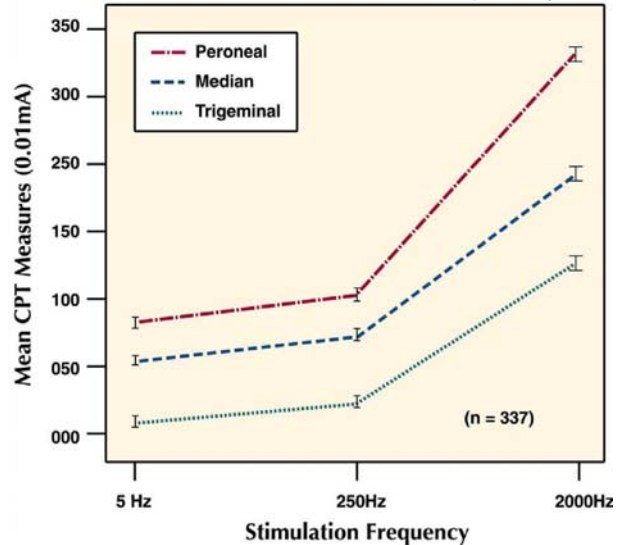
Sensory Nerve Fiber Types

Typical sensory nerves are composed of 3 major subpopulations of fibers. The large myelinated “A_β” fibers conduct cutaneous touch and pressure sensations, the small myelinated “A_δ” fibers conduct temperature, pressure and fast pain sensations while the small unmyelinated “C”-fibers comprising more than 80% of the total, primarily conduct temperature and slow pain sensations. The small myelinated, A_δ fibers and unmyelinated C fibers are responsible for conducting protective sensations that guard against serious injury. Unmyelinated C fibers also serve a critical role in the peripheral autonomic nervous system providing the innervation to the smooth musculature. One third of the C-fibers are autonomic efferents. Clinical implications of the loss of large fiber function are not as severe as a loss of smaller fiber function.

Neuroselective Pathology

Clinical complications resulting from C fiber polyneuropathy include foot ulceration, gangrene, cardiac and other types of autonomic dysfunction. The loss of protective function associated with small fiber “Painless” polyneuropathies is also associated with “Painless” myocardial infarction. Standard clinical evaluations ranging from the safety pin to the reflex hammer and sensory nerve conduction velocity tests do not evaluate C fiber function. The Neurometer provides an objective automated non-invasive painless neuroselective evaluation of C fiber as well as A_δ and A_β fiber functional integrity.

CPT Data: Site vs. Frequency



Both sensory and motor nerves are affected by metabolic polyneuropathy. Common polyneuropathies are associated with sensory symptoms and autonomic dysfunction occurring before weakness or motor impairment. Within the sensory nerve, various subpopulations of fibers have differential susceptibilities to different types of neuropathies.²²

“Painless Neuropathy”

Loss of Protective Sensation

“Painless Neuropathy” is characterized by the selective loss of smaller fiber protective sensation. An individual with this condition has intact large fiber touch sensation and may even be unaware of the neuropathy, greatly increasing the risk of serious injury. For example, the individual may feel the “touch” sensation of stepping on a burning cigarette but not the “protective” sensation of the burn. Due to pain insensitivity, complications from the foot burn may progress to infection and amputation. It is also important that the fingers be evaluated to determine the extent of this neuropathy.

C Fiber Neuropathy and Autonomic Dysfunction

The impairment of autonomic function resulting from C fiber neuropathy can be a risk factor for mortality among diabetic/uremic patients. The CPT evaluation has been reported by an NIH Consensus Conference to be a strong predictor of mortality among kidney dialysis patients.¹⁴

Neurometer[®] Electrodiagnostic Evaluation Neuroselectivity, Hyperesthesia and Pain

The Neurometer generates a constant alternating current (AC) stimulus to evoke nerve responses. The three major sub-populations of sensory nerve fibers are defined by their morphologic, electrophysiologic and functional (e.g. pain vs. non-pain transmission) characteristics. The smallest diameter unmyelinated fibers comprise greater than eighty percent of the total fibers, possess the longest refractory periods and the slowest average conduction velocities (CV) of 1 m/s. In contrast, large diameter myelinated fibers comprise less than ten percent of the total fibers, have the briefest refractory periods and fastest average CV of 60 m/s. Neuroselectivity is achieved by using three different frequencies of an electrical sinewave stimulus (2000 Hz, 250 Hz and 5 Hz), taking advantage of this waveform's frequency dependent rate of depolarization. Large diameter fibers can generate action potentials in response to the rapid 2000 Hz stimulus but small fibers require several milliseconds of continuous depolarization (i.e. low frequency stimulation, e.g., 5 Hz), to reach threshold potential. Large fibers will generate action potentials to the 5 Hz stimulus, but not at physiologically significant rates.¹⁶ Additionally, the quantity of electrons or charge per depolarization of a 5 Hz sinewave (100 msec) is 400 times the charge and duration of a 2000 Hz sinewave depolarization (0.25 msec). Together, these factors result in the 2000 Hz stimulus selectively evoking physiologically significant large myelinated fiber responses and the 5 Hz stimulus selectively evoking physiologically significant unmyelinated fiber responses.

The neuroselective nature of the sinusoid waveform electrical stimulus was first demonstrated in a study comparing the application of a variety of waveform types on healthy individuals at Johns Hopkins in the 1980's.¹⁵ Neurometer measures have been compared with the results of other physiological/imaging,¹⁶ diagnostic,¹⁷ histologic¹⁸ and pharmaceutical studies.¹⁹ These and other studies involving nerve regeneration,²⁰ ischemia²¹ and neuroselective pathological conditions²² have corroborated the neuroselective nature of this stimulus. The CPT measures also have the unique ability of evaluating pathologies such as hyperesthesia and hypoesthesia that may selec-

tively occur in one or more subpopulations of sensory fibers while sparing the others.

Hyperesthesia and Allodynia

Hyperesthesia, as measured by abnormally low neuroselective Current Perception Threshold (CPT) measures, reflects an increased electrical excitability of sensory nervous tissue for the evocation of responses. The resting membrane potential of the sensory nerve fiber increases as the result of stresses such as hyperglycemia.²³ An elevated resting membrane potential decreases the intensity of the excitatory electrical stimulus required to reach the threshold required to evoke an action potential response. In other words, less electrical energy is required to evoke a neuronal response.

Hyperesthesia is reported in the early stages of progressive neuropathy affecting both pre-diabetics and newly diagnosed diabetics.²⁴ Other early occurrences of hyperesthesia are present in alcoholism, Carpal Tunnel Syndrome (CTS) and radiculopathy. A different type of hyperesthesia results from chronic hereditary sensory neuropathies associated with lysosomal storage disorders and primary biliary cirrhosis, demyelinating polyneuropathies and infectious conditions (eg. HIV, Lyme Disease).²⁵ Other neurodiagnostic tests, (e.g. sensory nerve conduction velocity, quantitative tactile, vibration and thermal thresholds) are insensitive to the hyperesthetic condition which is often sub-clinical.

Pain Tolerance Threshold (PTT)

When the Neurometer stimulus is administered at intensities greater than the painless CPT sensory threshold it is possible to evoke painful sensation. Under patient control, the maximum tolerable intensity neuroselective stimulus is defined as the Pain Tolerance Threshold (PTT). The PTT has been demonstrated to be a reliable measure for the evaluation of pain and select analgesic agents. Allodynia is characterized by increased sensitivity to a non-noxious stimulus

which the subject characterizes as "painful". Allodynia may be evaluated by neuroselective Pain Tolerance Threshold (PTT) measures as well as the less painful "Percentile Allyodynia Test". CPT hyperesthesia and PTT allodynia may occur as neuroselective and independent sensory conditions.²⁶ For example, spinal opiates do not affect the 2000 Hz, 250 Hz or 5 Hz painless CPT measures or the 2000 Hz and 250 Hz PTT measures but they selectively elevate 5 Hz PTT measures in humans.^{19k} Similar Neurometer neuroselective response measures have been reported from rats.^{19l}

Direct Nerve Fiber Stimulation

Neurometer CPT and PTT measures are not receptor or end-organ mediated. The electrical stimulus bypasses the end-organs and directly excites the nerve fibers. Skin freeze or burn lesions precipitate the local release of an "inflammatory broth" (e.g. bradykinins, prostaglandins, leukotrienes, substance P, etc.) which bind to receptors resulting in local sensory thermal and tactile threshold changes. Thermal allodynia (pain evoked by normally painless heat stimulus) and tactile allodynia (pain evoked by a normally painless tactile stimulus, e.g., Von Frey filament stimulus) occurs with these lesions. Research has demonstrated that sNCT electrical allodynia, however, does not occur with the skin freeze model and other differences between these types of stimuli that may be due to their different site of stimulation, i.e., end-organ vs direct nerve stimulation.²⁷

fMRI and Neurometer Pain

Functional magnetic resonance imaging studies from the Massachusetts General Hospital have demonstrated that heat pain and 5 Hz sNCT pain increase metabolic activity in the same areas of the brain; however, there is a habituation to the heat pain stimulus that does not occur with the electrical pain stimulus. This and other fMRI related studies are cited.²⁸

Endnotes

The endnotes include representative examples from more than 600 peer reviewed publications utilizing Neurometer[®] technology. Additional documentation and bibliographies of publications are continuously updated at: www.neurotron.com.

1. Dermatology & Cosmetic Publications

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- C.) Ericson, M., Boeck, C. Hordinsky, M. Differences in the current perception thresholds (CPTs) of C nerve fibers in affected and unaffected scalp of patients with alopecia areata. Society for Investigative Dermatology, Poster No. 633, Montreal, 2009.
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- F.) Ertel, K., Watson, D., Bacon, R. Instrumental assessment of changes in skin susceptibility to neurosensory phenomena induced by personal care products. Presented at the American Academy of Dermatology, 66th Annual Meeting. Poster 904. Journal of the American Academy of Dermatology, Vol. 58 (2), 2008.
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- I.) Porcheron, A., Jdid, R., Nageotte, O., Guinot, C., Tschachler, E., Morizot, F., Modulation of Aβ nerve fibers perception by a daily use of a skin moisturizer. Intl. Derm. Euro. Abstract, 399;2008.
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- K.) Yokota, T., Matsumoto, M., Sakamaki, T., Hikima, R., Hayashi, S., Yanagisawa, M., Kuwahara, H., Yamazaki, S., Ogawa, T., Hayase Classification of Sensitive Skin and Development of a Treatment System Appropriate for Each Group. (International Federation of the Societies of Cosmetic Chemists) IFSCC Magazine, Vol 6(4):303-307, 2003.
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Differences in Itch Perception. Journal of the American Academy of Dermatology. Vol 55:996-1002, 2006.

2. Review Publications

- A.) Shigeki, F., Seiji, T. Review of Current Perceptual Threshold with Neurometer: Differences in the Shape of the Electrode. Journal of Japanese Dental Society of Anesthesiology. Vol.33;(2) 202-207, 2005.
- B.) Katims, J.J. Electrodiagnostic Functional Sensory Evaluation of the Patient with Pain: A Review of the Neuroselective Current Perception Threshold (CPT) and Pain Tolerance Threshold (PTT). Pain Digest Vol 8(5), 219-230, 1998.
- C.) Katims, J.J., Mitsuhashi, H., Miyazaki, T. Electrodiagnostic evaluation of sensory nerve function in the patient with pain: Neuroselective Current Perception Threshold (CPT) and Pain Tolerance Threshold (PTT). Pain Clinic (Japan), Vol 19(4):535-549, 1998.
- D.) Katims, J.J. Evaluation of Pain. 11th International Pain Clinic, World Congress of Pain Clinics (Tokyo) Medimond, S.r.l. Italy, 55-58, 2004.
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3. Regeneration/Transplantation: Recovery of Function (Also see Laboratory Animal Section)

- A.) Caissie, R., Gingras, M., Champigny, M., Berthod, F. In Vivo Enhancement of Sensory Perception Recovery in a Tissue-Engineered Skin Enriched with Laminin. Biomaterials. Volume 27(15):2988-2993, 2006.
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- C.) Nishimura, A., Ogura, T., Hase, H., Makinodan, A., Hojo, T.; Katsumi, Y., Yagi, K., Kubo, T. Evaluation of sensory function after median nerve decompression in carpal tunnel syndrome using the current perception threshold test. Journal of Orthopedic Science Vol 8:500-504, 2003.
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