



NEUROTRON, INCORPORATED

INNOVATIVE MEDICAL TECHNOLOGY

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May, 2004

Animal Research Using Neurometer® Technology

The Neurometer CPT/C diagnostic neurostimulator comes from the clinical world to the animal research laboratory¹. This device is capable of performing harmless assessments of sensory nerve and pain function in laboratory animals. Although a majority of the 400 publications with Neurometer® technology involve clinical studies, researchers have observed that mice are easier to test than people. Any animal response may be evaluated including vocalization, tail flick, paw withdraw as well as physiological parameters.

Key points about testing with Neurometer® Technology Include:

- Non-invasive, harmless stimulus permitting serial measures from the same site
- May be used to test any cutaneous or mucosal site on large or small animals. Evaluation of the concha of the ear gives direct access to brain stem neurons for CNS measures.
- Independently quantifies large and small myelinated and unmyelinated nerve fiber function
- Objective evaluation of therapies for nerve pathology (e.g., diabetes), neuro-protection, regeneration (e.g., repair and transplants), pain or toxic side effects (e.g., chemotherapy, alcohol, environmental)
- fMRI compatible
- Computer control program provides reliable and reproducible testing and data recording

The neuroselective nature of the sNCT/CPT stimulus permits each of the 3 sub-populations of sensory nerve fibers at the test site to serve as a with-in site control. This is helpful when evaluating neuroselective neuropathies (ex. demyelinating vs small fiber neuropathy), agents or conditions such as opiates and local anes-

thetics or nerve compression, vibration neuropathy and regeneration. The constant current stimulus is not effected by skin thickness variations. The electrical stimulus bypasses end-organs (e.g. thermal sensitive Ruffini corpuscles or vibration sensitive Pacinian corpuscles). This is consistent with reports that:

- Studies from the University of Vienna and Stanford University demonstrate that the Pain Tolerance Threshold (PTT) measure is insensitive to skin freeze lesions that change thermal pain tolerance thresholds.²
- fMRI studies from Massachusetts General Hospital and Harvard Medical School have show that the 5 Hz PTT and painful heat applied to the hand activate the same regions of the human brain with the exception that there is a rapid habituation to the thermal and not the electrical stimulus.³

Neurometer® Animal Response Testing Control Program

The Animal Response Test (ART) is conducted using the CPT/C Computer Control & Automation Software Program. This automation program is necessary for the customization and standardization of the Neurometer® CPT/C stimulus for animal research and may be used alone or in conjunction with other computer control programs including fMRI systems. Customized fMRI electrode cables are available from Neurotron, Inc.

One or Two Group Study Designs

Animal response research studies to evaluate the effects of a therapeutic intervention, when normative values have not been previously established, may be conducted using one or two groups of animals.

One Group Study: Animals are tested with a matched control site, for example a study of a

nerve regeneration where one hind paw may be compared to another or comparing hind paw to forepaw in spinal animals.

Two Group Study: The treatment group is evaluated before, and during and possibly after an intervention. The second matched group is tested at similar times using a sham intervention.

Animal Testing: Cutaneous Electrode Placement

- The testing requires the application of a minimum of 2 electrodes. A stimulation electrode and a dispersion return electrode.
- Generally, the stimulating electrode is placed at sites without significant underlying musculature such as the distal phalanges, tail, pinna or over the mastoid. Placement of the electrode on the concha of the ear permits direct evaluation of brainstem sensory function via the vagus nerve. These placements prevent the possibility of electrically evoking muscle twitches under the stimulating electrode during the testing.
- Two options for stimulating electrodes are available.
 - a) A square shaped 4mm x 4 mm silver electrode.
 - b) A round 1 cm. diameter gold electrode.
- The self sticking dispersion electrode is typically placed on the skin. Because the surface area of this electrode is much greater than the stimulating electrode, the current density remains so low that the underlying nerves do not receive adequate stimulus to evoke a response - even at the maximum stimulus output of 10 or 20 mAmps.

An easy application site for the dispersion electrode is the proximal tail. The electrode may be wrapped around the proximal tail and stuck to itself to stay in place. Alternatively, it may be placed on the flank or back of a small animal (mouse, rat or rabbit).

- The most sensitive site for detecting distal axonal polyneuropathy in a diabetic lab rat would be the tip of the tail. Any rats with diabetic neuropathy that includes diffuse demyelination could be excluded from the

study by testing at the proximal tail, paw or other proximal site.

- A comfortable restraint system for the animal to prevent chewing through the electrode cable during testing is recommended.

Information on the Neurometer® Computer Control and Automation Software used for animal studies is available upon request or at http://neurotron.com/p_ctrl-1.html.

A listing of Clinical and Laboratory & Animal related publications using Neurometer® technology is included in the Neurometer® *Abstract Booklet* available upon request and from <http://neurotron.com/downloads.html#absB>.

Please contact Neurotron, Inc. for additional information or references regarding animal testing using the Neurometer CPT/C device.

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 2. Lötsch J, Angst MS. The mu-opioid agonist remifentanyl attenuates hyperalgesia evoked by blunt and punctuated stimuli with different potency: a pharmacological evaluation of the freeze lesion in humans. Pain Volume 102:151-161, 2003.
 3. Bocerra, L., Stojanovic, M., Chang, I., Breiter, H., Tracey, I., Fishman, S., Edwards, A., Gonzalez, R.G., Borsook, D. fMRI Mapping of CNS Activation Following Noxious Heat and Electrical Stimuli. Fifth Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Vancouver, 1997. Stojanovic, M., Becerra, L.R., Breiter, H.C., Fishman, S.M., Edwards, A., Chang, I.W., Borsook, D., Gonzalez, G. fMRI Analysis of Human CNS Activation Following Noxious Electrical Stimulation at 5 Hz and 250 Hz. Annual Meeting of the American Pain Society, New Orleans, LA, 1997.