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# Changes in measures of motor axon excitability with age

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**Abstract**

*Objective:* Threshold tracking is a novel technique that permits examination of the excitability of human axons *in vivo*. Protocols have been validated for sensory and motor axons, but there are limited data on the changes in the excitability of motor axons with age. This study aimed to determine such changes from the third to the eighth decades.
*Methods:* Sixty healthy subjects aged 22–79, 10 per decade, were studied using the TRONDXM4 protocol of the QTRAC threshold-tracking program to assess motor axon function. The median nerve was stimulated at the wrist and the compound muscle action potential was recorded from the thenar muscles.
*Results:* There was an increase in threshold in elderly subjects, associated with a decrease in slope of the stimulus–response curves. Strength-duration time constant and threshold electrotonus to depolarising and hyperpolarising currents of up to 40% did not change significantly with aging. The current–threshold relationship was similar across all decades for subthreshold depolarising currents, but the slope of the current–threshold relationship was significantly steeper the older the subjects for hyperpolarising currents, particularly those greater than 40% of threshold. There was also a significant decrease in supernormality in the recovery cycle with increasing age.
*Conclusions:* The threshold of axons increases with age and the extent of supernormality decreases. There may also be greater inward rectification in motor axons, perhaps due to greater activity of $I_H$, the hyperpolarisation-activated conductance, though this is only significant with hyperpolarising currents greater than 40% of the threshold current.
*Significance:* Many indices of axonal excitability, such as strength-duration time constant, the relative refractory period, late subnormality, threshold electrotonus and the depolarising side of the current–threshold relationship, do not change significantly with age. For other indices, age-related changes may be due to a combination of non-neural factors that alter current access to the node of Ranvier, changes in the axon and its myelination and, possibly, changes in channel activity and/or changes in extracellular $[K^+]_o$.


*Keywords:* Axonal excitability; Age; Threshold tracking; Supernormality; Inward rectification

## 1. Introduction

Changes occur throughout the peripheral nervous system with age. For example, age-related structural changes include neuronal loss in the dorsal and ventral columns (Kawamura et al., 1977; Tomlinson and Irving, 1977), fibre loss in peripheral nerves, especially thick myelinated fibres, and changes in internodal length (Lascelles and Thomas, 1966; Jacobs and Love, 1985; Vital et al., 1990). The importance of these changes increases with age, becoming noticeable in the fifth decade and significant in the seventh. A reduction in the number and density of human myelinated fibres with old age has been demonstrated in spinal roots (Kawamura et al., 1977) and in the radial (O'Sullivan and Swallow, 1968), ulnar (Rafalowska et al., 1976), sciatic (Takahashi, 1966), peroneal (Stevens et al., 1973), tibial (Swallow, 1966) and sural nerves (O'Sullivan and Swallow, 1968; Jacobs and Love, 1985). There are also changes in peripheral motor unit function with age: muscle mass/area is reduced and there may be an increase in slow (type I) muscle fibres compared to fast (type II) fibres. Motor force

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and strength are reduced by 20–40% in subjects after the age of 70 although changes are observed from the sixth decade. A single motor axon innervates more muscle fibres, producing polyphasia on macro EMG (see Roos et al., 1997 for review). Touch-pressure, vibratory and cooling detection thresholds increase with age, and there is a reduction in the density and size of Meissner corpuscles in the fingers (Bolton et al., 1966) and the plantar surface of the big toe (Schimrigk and Rüttinger, 1980). The threshold for perception of electrical stimuli increases with age (Nadler et al., 2002).

Axonal excitability studies using threshold tracking are a recent addition to the neurophysiological armamentarium available to assess peripheral nerve function. They are now being employed to determine changes in excitability of axons in various pathologies to help determine the underlying pathophysiology. There has been, so far, no systematic analysis of age-related changes in the different measures of the excitability of motor axons, apart from a recent study showing no significant correlation between strength-duration time constant and age (Tamura et al., 2006). There has also been a study that documented the changes in excitability of sensory axons with age (Kiernan et al., 2001). Many pathologies affect only the elderly or are more severe the older the subject, and it is therefore relevant whether different excitability indices vary with age. This study was undertaken to determine if excitability indices of motor axons change with age, to determine the relationship with age and, hopefully, to shed light on the mechanisms.

## 2. Methods

### 2.1. Subjects

Nerve excitability studies were performed on motor axons in 60 subjects of both genders, from 22 to 79 years, 10 per decade, 28 males and 32 females (Table 1), using the protocol and techniques described in full elsewhere (Bostock et al., 1998; Kiernan et al., 2000). The subjects provided informed consent to the procedures that had the approval of the Human Research Ethics Committee of the University of Sydney. For all experiments, skin temperature was monitored close to the stimulation site and was maintained above 32 °C using blankets.

The median nerve was stimulated via non-polarisable electrodes (Maersk Medical, Stonehouse, UK) with the cathode over the median nerve at the wrist and the anode 10 cm proximal over muscle on the radial aspect of the arm. Compound muscle action potentials (CMAPs) were recorded from thenar muscles using surface electrodes over abductor pollicis brevis (APB) with the active electrode at the motor point and the reference electrode on the proximal phalanx. The electromyographic (EMG) signal was sampled at a rate of 10 kHz, amplified, filtered (3–500 Hz), and digitized by computer (Pentium PC) with an analogue-to-digital board (DT2812, Data Translation, Marlboro, Massachusetts). Stimulus waveforms were generated by the computer and converted to current by an isolated linear bipolar constant-current source (maximal output ± 50 mA).

Motor axons were studied using the multiple excitability protocol, TRONDXM4 (QTRAC version 8.2, ©Professor H. Bostock, Institute of Neurology, London), as described elsewhere (Kiernan et al., 2000). Test current pulses of 0.2- or 1-ms duration were delivered regularly at 0.8-s intervals to produce a target potential that was on the fast rising phase of the stimulus–response curve, ~40% of the maximal CMAP. The computer was programmed to maintain the test potential at this target size despite changes in stimulus duration or the delivery of conditioning stimuli, either suprathreshold stimuli or subthreshold polarising currents. The amplitude of the CMAP was measured from baseline to the negative peak. Stimulus–response curves were recorded separately for test stimuli of 0.2- and 1-ms duration. These data were used to optimise threshold tracking (Kiernan et al., 2000) and to calculate the strength-duration time constant ($\tau_{SD}$) according to Weiss' Law, based on the linear relationship between stimulus charge (mA × ms) and stimulus duration. The $\tau_{SD}$ is a nodal property and reflects the rate of decrease of threshold current as the duration of the stimulus pulse increases.

Prolonged subthreshold currents were used to alter the potential difference across the internodal membrane. The changes in threshold associated with electrotonic changes in membrane potential are termed threshold electrotonus and generally reflect the underlying changes in membrane potential. The subthreshold polarising currents were of 100-ms duration and set to be +40% and +20% (depolarising) and −40% and −20% (hyperpolarising) of the control

Table 1
Demographics and nerve conduction indices

| Decade | Mean age (range) | Sex ratio M:F | CMAP amplitude (mV) | Onset latency (ms) | Mean threshold 50% CMAP (mA) |
|---|---|---|---|---|---|
| 20–29 | 26.3 (22–29) | 6:4 | 8.53 ± 0.92 | 2.78 ± 0.11 | 8.49 ± 0.71 |
| 30–39 | 31.4 (30–35) | 3:7 | 9.88 ± 1.05 | 2.80 ± 0.08 | 8.90 ± 0.74 |
| 40–49 | 42.8 (41–47) | 5:5 | 10.05 ± 0.92 | 2.64 ± 0.12 | 9.73 ± 1.61 |
| 50–59 | 54.7 (50–59) | 5:5 | 8.46 ± 0.72 | 2.80 ± 0.12 | 10.39 ± 1.53 |
| 60–69 | 63.4 (50–59) | 3:7 | 9.27 ± 1.08 | 3.03 ± 0.12 | 12.24 ± 1.91 |
| 70–79 | 74.5 (70–79) | 6:4 | 9.53 ± 1.00 | 4.03 ± 0.20 | 15.83 ± 1.64 |
| Change with age | | | No significant change | Quadratic $R^2 = 0.21$, $P = 0.001$ | Quadratic $R^2 = 0.24$, $P < 0.001$ |

Data are mean ± SEM.