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SHORT COMMUNICATION
Neural substrates of microstimulation-evoked tingling: a chronaxie study in human somatosensory thalamus

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Abstract

Intra-operative micro-electrode stimulation of sensorimotor thalamus produces paraesthesia or tingling in various body regions and is used to map somatotopy prior to implantation of deep brain-stimulating electrodes in awake patients. The neural elements affected by such microstimulation are unknown. Using paraesthesia as the behavioural–physiological response threshold, we measured chronaxie times for microstimuli applied to both somatosensory thalamic nuclei (cellular region) and its axonal afferents, the medial lemniscus. White matter chronaxie times were relatively unimodal, whereas two different clusters of chronaxie times were identified in grey matter: one corresponding to that of the medial lemniscus and the other about five times longer and compatible with that obtained from cell somata. Therefore, excitations of local axons and/or cell bodies can both contribute to the paraesthesia evoked during intra-operative thalamic mapping.

Introduction

Electrical stimulation of sensorimotor thalamus via a microrecording electrode is routinely utilized in the operating room for delimiting the boundaries of sensory thalamus and for determining optimal loci of tremor stoppage (Tasker & Kiss, 1995). Despite broad adoption of this technique, the neural elements that are activated during a brief microstimulation are not clearly known and remain controversial. Macrostimulation of the thalamus via large chronically implanted deep-brain-stimulating (DBS) electrodes seems to suggest that the stimulation (chronaxie) time required for evoking an electromyographic response is short and invariable (Ashby *et al*., 1995), thus consistent with the hypothesis that large-diameter myelinated axons are responsible for stimulation effects. Similar chronaxie times have also been obtained for macrostimulation induced for tremor stoppage (Holsheimer *et al*., 2000). Such unimodal short chronaxie times have not been verified for microelectrode-based stimulations, despite the theoretical 4000 times difference in current spread between the two stimulation methods (Wu *et al*., 2001). The goal of our study was to obtain a better understanding of the physiological mechanism underlying microstimulation and chronaxie time measurements, which are widely utilized in studying human neurophysiology. We therefore applied microstimulation within either cellular or white matter regions and measured chronaxie times of neural activation that are required for an alert patient to report paraesthesia. A comparison of the chronaxie times indicates that excitations of local axons and/or cell bodies may both contribute to the paraesthesia evoked during intra-operative thalamic mapping.

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Materials and methods

Patients who had micro-electrode exploration of thalamus and globus pallidus pars interna (GPi) prior to insertion of DBS electrodes were studied. Each patient underwent postoperative magnetic resonance imaging confirming appropriate placement of their lesion or DBS macro-electrode. This protocol was part of that approved by the Conjoint Health Region Ethics Board for intra-operative collection of data. Details of the methods used for micro-electrode recording and stimulation have been reported elsewhere (Tasker & Kiss, 1995). Stimulation was applied with a monophasic constant-current stimulus isolator in combination with a stimulus generator (A360 and A310, WPI, Sarasota, USA) using micro-electrodes (UEI-ME1, Universal Electrodes, Dothan, USA) with exposed tips of 25 μm (0.2–0.5 MΩ at 1000 Hz). Cathodal pulses were provided at the electrode tip and referenced to the guide tube containing the micro-electrode.

Tactile thalamus (ventrocaudal nucleus, Vc, according to Hassler's nomenclature; Schaltenbrand & Wahren, 1977) and medial lemniscus were explored in six patients undergoing thalamic DBS (Tasker & Kiss, 1995), as was the optic tract in one patient who had GPi-DBS surgery (Lozano *et al*., 1996), as part of the usual brain mapping procedure. The optic tract is identified as the acellular region below the GPi where patients experience visual phosphenes when current is passed through the micro-electrode or a flashing light elicits evoked potentials measured with the micro-electrode (Lozano *et al*., 1996). The Vc nucleus is the region of cellular thalamus where the micro-electrode encounters many neurons with small tactile receptive fields on the contralateral body, face and limbs. When stimulation is applied in awake patients through the micro-electrode, they experience paraesthesia in isolated small projected fields on the body, often at the same site as that of the nearby cells' receptive field (Davis *et al*., 1996). Below Vc is the medial lemniscus, an acellular or sparsely cellular zone where microstimulation elicits hemibody or large multilimb

projected fields at low threshold (<40 μA, using 300 Hz, 0.2-ms pulse width) (Tasker *et al*., 1982; Tasker & Kiss, 1995).

When our micro-electrode passed through a known tactile region of thalamus, medial lemniscus or optic tract the following protocol was undertaken. Patients were awake and alert during this procedure as they received no sedation on the day of surgery. Microstimulation was applied at 100 Hz, 1-s train duration, progressively decreasing the pulse width from 5000 to 5 μs. The current was increased initially by factors of 1, then 2, and finally 5-μA steps to a maximum of 100 μA until the patient reported the perception of tingling. As they were already familiar with the sensations elicited by microstimulation at other sites during the course of the operative procedure, the patient was simply asked to report when they first felt paraesthesia for each pulse width applied. An interval of at least 3 s was allowed between each stimulus application, and some sites were repeatedly checked by reducing the interval between current steps applied, coming from both suprathreshold and subthreshold current amplitudes to determine the true threshold for perception. Although the location and nature of the paraesthesia reported by the patients sometimes did change slightly during the progressive decrease in pulse durations applied, owing to

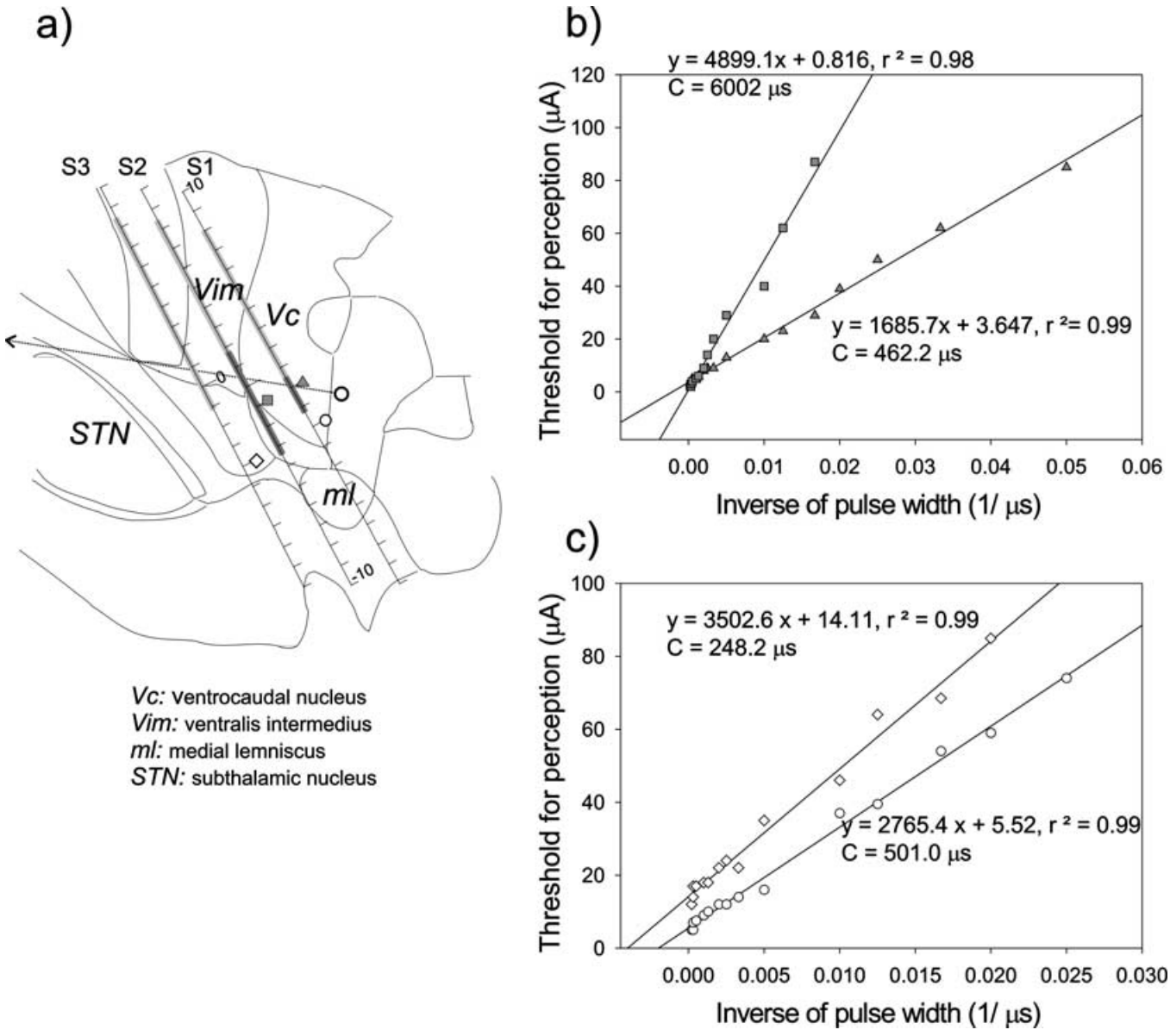

FIG. 1. Representative example of the sites and chronaxie times measured in a patient with essential tremor. (a) Reconstruction of micro-electrode trajectories and sites where the experimental protocol was performed. Note that the 15-mm lateral section from the Schaltenbrand & Wahren (1977) human brain atlas is shown with the anterior–posterior commissure (dotted black line with arrow towards the anterior commissure) stretched to fit coordinates obtained from the patient's stereotactic imaging. The lines, labelled S1–3, passing through the map indicate the locations of the micro-electrode trajectories and are not corrected for physiological findings. The light grey thick line indicates the cellular regions encountered with micro-electrode recording. The dark grey heavy line shows the tactile Vc region. The symbols indicate the sites where pulse duration testing was performed. (b) Graph of the method used to calculate chronaxie times, using the inverse of pulse width vs. threshold to elicit paraesthesia in tactile Vc nucleus. The same symbols are used as are shown in the map in (a). The regression line for each site is shown with the regression coefficient, the linear equation representing the line and the chronaxie time (*C*) determined from the slope/intercept of the line. (c) Curves obtained from microstimulation in the medial lemniscus in the same patient.

time limitations in the operating room no attempts were made to differentiate them systematically during the testing protocol. To compare chronaxie times measured using the micro-electrode to that obtained from the DBS macro-electrode, the same protocol was repeated postoperatively in three patients using the DBS electrode (resistance of 1–2 kW) to apply current amplitudes from 0.1 to 10 mA and also measuring behavioural thresholds to paraesthesia.

The analysis performed to determine chronaxie times involved plotting graphically the inverse of the pulse width (x-axis in units of 1/μs) to the threshold for paraesthesia (y-axis in units of μA) for each site. Graphs with regression coefficients of >0.90 were considered linear and the slope and y-intercept used to calculate the chronaxie time (C) where $C =$ slope/intercept. The chronaxie data from grey and white matter were both fit with a nonlinear regression model, assuming consistent Gaussian scatter (GraphPad Software Inc.). A runs test was used to determine goodness of fit with significance set at $P = 0.05$. Grubbs' test was used to check for outliers. The Mann–Whitney rank sum test was then used to compare data from grey and white matter (SigmaStat 2.0, Jandel Scientific). Results are reported as mean ± standard deviation (SD).

Results

A total of 19 sites were tested intra-operatively in seven patients. A representative example of how chronaxie times were measured in one patient is shown in Fig. 1. Using Grubbs' test, only one site in the medial lemniscus was eliminated as an outlier ($P < 0.05$), leaving nine sites in the medial lemniscus, one site in the optic tract and eight sites in the Vc tactile thalamus. In the medial lemniscal, the mean chronaxie times were 668 (± 300) μs. The chronaxie time measured at one site in the optic tract was 335 μs. The distribution of chronaxie times obtained from white matter could be best fitted by a Gaussian distribution ($P = 0.2$, Runs test), suggesting a homogeneous data set. By contrast, the chronaxie time measured in cellular thalamus exhibited large variabilities, which could not be fitted by a Gaussian distribution. Instead, as shown in Fig. 2, the data can be presented as two significantly different data populations ($P < 0.0001$, unpaired t-test with or without Welch's correction). One population had a mean value of 798 (± 318) μs, corresponding to that of white matter, and the other population was significantly longer (5903 ± 141 μs) and closer to that reported for soma (Ranck, 1975). As expected, when the two data groups were amalgamated and compared with white matter, no statistical difference was found ($P = 0.12$, t-test).

Chronaxie times, measured using the chronic DBS electrode and using thresholds for paraesthesia, yielded a result of $C = 189 \pm 71$ μs ($n = 3$ patients) consistent with previous reports using thresholds to EMG response (Strafella *et al.*, 1997) or tremor suppression (Holsheimer *et al.*, 2000).

The location and nature of the paraesthesia reported by the patients sometimes did change slightly during the progressive decrease in pulse duration applied. In one case, below the cellular thalamus in presumed medial lemniscus, pulse widths of 5000 μs elicited an auditory sensation whereas with pulse widths < 500 μs somatosensory tingling was reported. In another case, hemibody pain at 5000 μs pulse width was replaced by coolness in the hand at 3000 μs and tingling in the hand and leg at 1000 μs.

Discussion

Chronaxie time has been utilized clinically as a physiological measurement for estimating the neural elements that are activated by extracellular electrical current (Holsheimer *et al.*, 2000; Grill & McIntyre, 2002). For a given element, the chronaxie time is mainly determined by the physical nature of the neural element (membrane excitability, surface-to-volume ratio, etc.) (Ranck, 1975) and its distance to the current source in a volume conductor (McIntyre & Grill, 1999). It has been reported that large-diameter myelinated axons have chronaxie times ranging from 50 to 100 μs (Ranck, 1975) and 30 to 200 μs (Holsheimer *et al.*, 2000), and neuronal cell bodies and dendrites have chronaxie times ranging from 1 to 10 ms (Ranck, 1975) or even up to 30 ms (Nowak & Bullier, 1998). The chronaxie times of grey matter were reported by Nowak & Bullier (1998) as being 380 ± 191 μs, whereas Ranck (1975) in his review of the literature determined that grey matter consisting of 'unknown elements' had chronaxie times in the range 200–700 μs. Interpretations of chronaxie times are further confounded by additional factors. First, the chronaxie times reported for soma and dendrites have been established using intracellular pulses that cannot be readily extrapolated to extracellular stimuli (Ranck, 1975; Nowak & Bullier, 1998). Secondly, data reported in the literature use either motor response as the physiological threshold in humans or action potential generation in animals. These are largely based on stimulation through a macro-electrode, which in the case of humans is a 1.5 × 1.2-mm DBS electrode (Ashby *et al.*, 1995; Holsheimer *et al.*, 2000). Data derived from micro-electrode stimulation and physiological mapping of sensory thalamus are scarce. The two stimulation methods may result in significantly different results (see below). Thirdly, few studies have attempted to correlate chronaxie times with sensory perception, although understanding the neural elements that are involved in a subjective percept, such as tingling, has important physiological implications (Libet *et al.*, 1967). It is in these aspects that our study has provided original findings.

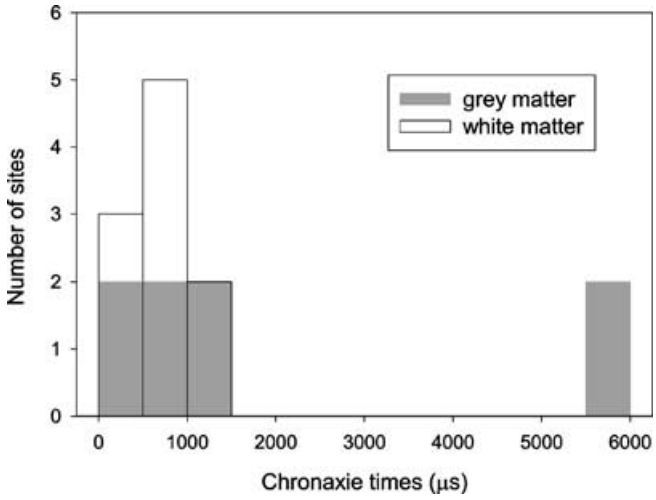

FIG. 2. Distribution of chronaxie times measured in grey and white matter with cathodal stimulation through the micro-electrode. The grey matter chronaxie times ($n = 8$) are shown overlying the white matter times ($n = 10$). There are two peaks of chronaxie times measured in grey matter, the shorter one being consistent with that measured in white matter and the second closer to that reported for soma.

Our microstimulation in the cellular thalamus and in the medial lemniscus revealed highly variable chronaxie times, albeit not completely random. Our data suggest that there may be at least two distinct ranges of chronaxie in grey matter. By comparing chronaxie with that in the medial lemniscus, we were able to show the fast excitation (i.e. shorter chronaxie times) is very similar to white matter excitation whereas the slower components had significantly

longer chronaxie times, which may correspond to activation of soma and/or dendrites. Questions, however, remain as to whether two excitation thresholds are caused by different axonal elements (i.e. axon hillocks vs. myelinated trunks; Gustafsson & Jankowska, 1976), or even differences in psychophysical awareness. Although our experiments cannot differentiate various axonal elements, we do not believe that fluctuation in psychophysical threshold is a major factor. This is because we tested both medial lemniscus and cellular thalamus in the same subjects who maintained similar levels of alertness during the procedure.

Furthermore, the chronaxie times we measured in white matter are longer than those reported by others in rat internal capsule (Nowak & Bullier, 1998) and peripheral nerve (Ranck, 1975). This difference, besides species, probably reflects the location of the micro-electrode in relation to nodes of Ranvier, and a mix of varying axonal diameters and degrees of myelination of axons passing through the prelemniscal and lemniscal radiations ventral to the Vc thalamus.

We and others have reported that chronaxie times measured using macrostimulation through the DBS electrode (about 100–200 μs; Strafella *et al*., 1997) are several orders of magnitude shorter than those obtained with the micro-electrode. One possible reason for this difference is that macrostimulation, which has a current spread several thousand times larger than the micro-electrode (Wu *et al*., 2001), may simultaneously excite a larger number of neural elements even with shorter pulse widths than microstimulation. This 'spatial' summation of excitation is sufficient to cause tingling. However, microstimulation needs to be applied for a much longer period of time in order to recruit an equal number of local neural elements to elicit the same response. Further studies are needed to test this 'spatial' vs. 'temporal' summation hypothesis.

The results described in this study have important implications. Different chronaxie times of various neural elements may not only be used to differentiate the cellular- vs. axonal-rich regions of the sensory thalamus during functional mapping, but may also explain why different sensory responses can be elicited from the same stimulation site. For instance, because microstimulation often excites axon elements and not necessarily the cell bodies being recorded with the micro-electrode, it may partially explain the mismatch between receptive fields and projected fields in humans with dystonia (Lenz & Byl, 1999). For other conditions, such as pain, the mismatch (Davis *et al*., 1998; Lenz *et al*., 1998) mechanism may be more complex owing to the presence of chronic de-afferentation and rebalance of local inhibitory and excitatory receptors (Rausell *et al*., 1992b). In our study, which did not include pain patients, one subject described a clear change in the sensations elicited by microstimulation at the same lemniscal site: paraesthesia changed to cold and then pain with progressively longer pulse durations. The simplest explanation for such transformation of subjective sensory perception at a single stimulus site is that fibre pathways for different sensations have different excitation thresholds but are co-localized on their way to the sensory thalamus (Rausell *et al*., 1992a). This is consistent with the fact that smaller fibres subserving pain and temperature require higher pulse durations to activate. It also suggests that these fibres may be contributing to the pain sensations evoked during human thalamic micro-electrode exploration (Lenz *et al*., 1993, 1998). Finally, because excitation of axonal fibres seems to be a major outcome of intrathalamic stimulation in both grey and white matter, one would expect that the therapeutic action of DBS electrodes may depend upon changes in both local thalamic neurons (via transmitter release) (Kiss *et al*., 2002; Anderson *et al*., 2003) and/or remote sites outside of the thalamus (i.e. cortex and cerebellum) (Deiber *et al*., 1993; Perlmutter *et al*., 2002).

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Abbreviations

DBS, deep-brain-stimulating; GPi, globus pallidus pars interna.

References

Anderson, T., Hu, B. & Kiss, Z.H.T. (2003) Synaptic mechanism of deep brain stimulation (DBS) in thalamus. *Stereotact. Funct. Neurosurg.*, in press.

Ashby, P., Lang, A.E., Lozano, A.M. & Dostrovsky, J.O. (1995) Motor effects of stimulating the human cerebellar thalamus. *J. Physiol. (Lond.)*, **489**, 287–298.

Davis, K.D., Kiss, Z.H.T., Luo, L., Tasker, R.R., Lozano, A.M. & Dostrovsky, J.O. (1998) Phantom sensations generated by thalamic microstimulation. *Nature*, **391**, 385–387.

Davis, K.D., Kiss, Z.H.T., Tasker, R.R. & Dostrovsky, J.O. (1996) Thalamic stimulation-evoked sensations in chronic pain patients and in non-pain (movement disorder) patients. *J. Neurophysiol.*, **75**, 1026–1037.

Deiber, M.-P., Pollak, P., Passingham, R., Landais, P., Gervason, C., Cinotti, L., Friston, K., Frackowiak, R., Mauguière, F. & Benabid, A.L. (1993) Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. *Brain*, **116**, 267–279.

Grill, W.M. & McIntyre, C.C. (2002) Extracellular excitation of central neurons: implications for the mechanisms of deep brain stimulation. *Thalamus Related Systems*, **1**, 269–277.

Gustafsson, B. & Jankowska, E. (1976) Direct and indirect activation of nerve cells by electrical pulses applied extracellularly. *J. Physiol. (Lond.)*, **258**, 33–61.

Holsheimer, J., Demeulemeester, H., Nuttin, B. & de Sutter, P. (2000) Identification of the target neuronal elements in electrical deep brain stimulation. *Eur. J. Neurosci.*, **12**, 4573–4577.

Kiss, Z.H.T., Mooney, D., Renaud, L. & Hu, B. (2002) Neuronal response to local electrical stimulation in rat thalamus: physiological implications for the mechanism of action of deep brain stimulation. *Neuroscience*, **113**, 137–143.

Lenz, F.A. & Byl, N.N. (1999) Reorganization in the cutaneous core of the human thalamic principal somatic sensory nucleus (ventral caudal) in patients with dystonia. *J. Neurophysiol.*, **82**, 3204–3212.

Lenz, F.A., Gracely, R.H., Baker, F.H., Richardson, R.T. & Dougherty, P.M. (1998) Reorganization of sensory modalites evoked by microstimulation in region of the thalamic principal sensory nucleus in patients with pain due to nervous system injury. *J. Comp. Neurol.*, **399**, 125–138.

Lenz, F.A., Seike, M., Richardson, R.T., Lin, Y.E., Baker, F.H., Khoja, I., Yeager, C.J. & Gracely, R.H. (1993) Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *J. Neurophysiol.*, **70**, 200–212.

Libet, B., Alberts, W.W., Wright, E.W. Jr & Feinstein, B. (1967) Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science*, **158**, 1597–1600.

Lozano, A.M., Hutchison, W.D., Kiss, Z.H.T., Tasker, R.R., Davis, K.D. & Dostrovsky, J.O. (1996) Methods for microelectrode-guided posteroventral pallidotomy. *J. Neurosurg.*, **84**, 194–202.

McIntyre, C.C. & Grill, W.M. (1999) Excitation of central nervous system neurons by nonuniform electric fields. *Biophys. J.*, **76**, 878–888.

Nowak, L.G. & Bullier, J. (1998) Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. *Exp. Brain Res.*, **118**, 477–488.

Perlmutter, J.S., Mink, J.W., Bastian, A.J., Zackowski, K., Hershey, T., Miyawaki, E., Koller, W. & Videen, T.O. (2002) Blood flow responses to deep brain stimulation of thalamus. *Neurology*, **58**, 1388–1394.

Ranck, J.B. (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.*, **98**, 417–440.

Rausell, E., Bae, C.S., Viñuela, A., Huntley, G.W. & Jones, E.G. (1992a) Calbindin and parvalbumin cells in monkey VPL thalamic nucleus: distribu-

tion, laminar cortical projections, and relations to spinothalamic terminations. *J. Neurosci.*, **12**, 4088–4111.

Rausell, E., Cusick, C.G., Taub, E. & Jones, E.G. (1992b) Chronic deafferentation in monkeys differentially affects nociceptive and nonnociceptive pathways distinguished by specific calcium-binding proteins and down-regulates gamma-aminobutyric acid type A receptors at thalamic levels. *Proc. Natl Acad. Sci. USA*, **89**, 2571–2575.

Schaltenbrand, G. & Wahren, W. (1977) *Atlas for Stereotaxy of the Human Brain*. Thieme, Stuttgart.

Strafella, A., Ashby, P., Munz, M., Dostrovsky, J.O., Lozano, A.M. & Lang, A.E. (1997) Inhibition of voluntary activity by thalamic stimulation in man: relevance for the control of tremor. *Mov. Disord.*, **12**, 727–737.

Tasker, R.R. & Kiss, Z.H.T. (1995) The role of the thalamus in functional neurosurgery. *Neurosurg. Clin. N. Am.*, **6**, 73–104.

Tasker, R.R., Organ, L.W. & Hawrylyshyn, P.A. (1982) *The Thalamus and Midbrain of Man. A Physiological Atlas Using Electrical Stimulation* Thomas, Springfield, Illinois.

Wu, Y.R., Levy, R., Ashby, P., Tasker, R.R. & Dostrovsky, J.O. (2001) Does stimulation of the GPi control dyskinesia by activating inhibitory axons? *Mov. Disord.*, **16**, 208–216.