Case Studies in Neuroscience: Evidence of motor thalamus reorganization following bilateral forearm amputations

Authors & Contributions:

*Benjamin P. Whatley[1]
- case review, data analysis, drafting of manuscript, figure & video preparation

Jeremy Chopek[3]
- data analysis, review of manuscript

Ron Hill[2]
- data collection, review of manuscript

Robert M. Brownstone[2,3]
- surgery and recording, report conception, feedback on data analysis, review and editing of manuscript.

Affiliations:

[1] Department of Medicine (Neurology), Dalhousie University, Halifax, Canada

[2] Department of Surgery (Neurosurgery), Dalhousie University, Halifax, Canada

[3] Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, Queen Square, London, United Kingdom WC1N 3BG

Running Head:

Motor thalamus reorganization following forearm amputations

*Address for correspondence:

Ben Whatley
Department of Medicine (Neurology), Dalhousie University
QEII – Halifax Infirmary Site
1796 Summer Street, Suite 3822
Halifax, Nova Scotia
Canada B3H 3A6

Email: bwhatley@dal.ca
Phone: (902) 449-1969

Abstract

Following injury, functional improvement can result from central nervous system plasticity. Use-dependent plasticity of motor systems is evident, for example, in recovery of function resulting from rehabilitative interventions. Here, we present a single patient who underwent bilateral microelectrode-guided stereotactic implantation of deep brain stimulating leads for the treatment of essential tremor 52 years following bilateral arm amputations. The tremor affected his upper extremities, and had rendered him unable to perform fine motor tasks with his prostheses, significantly reducing his independence. We found a large territory of neurons in the ventral intermediate nucleus of his thalamus that responded to shoulder protraction, the movement that he used to control fine motor movements of his terminal hook prostheses. We propose that reorganization of this motor nucleus may have occurred secondary to a use-dependent gain of function in neurons that were previously involved in hand movement.

Keywords: Neuroplasticity, Tremor, Movement Disorder, Deep brain stimulation

Introduction

Neural circuits for movement are remarkably adaptable. Evidence for this can be seen in people who have suffered acquired brain injuries, who with therapy and training recover significant motor function (Dimyan and Cohen 2011). However, the corresponding sites of motor circuit adaptive changes are not clear, and could include the cerebrum, diencephalon, cerebellum, brain stem, and/or spinal cord.

Following limb amputation, there is evidence of neuroplastic changes in sensory nuclei of the thalamus. Previous observations in the context of post-amputation phantom pain in humans (eg. (Davis et al. 1998)), as well as from experimental animal studies (eg. (Rasmusson 1996)), have demonstrated that there is expansion of receptive fields (brain regions that respond to somatic sensory stimulation) in the sensory thalamus arising from the amputation stump. Projected fields (somatic regions where sensation is felt during brain stimulation) involving the amputated limb may also be expanded and overlap with receptive fields of the stump. But whether there are also changes in diencephalic motor regions is not known. The absence of evidence for such reorganisation likely reflects the absence of recordings from motor regions of the human thalamus in patients with amputation, as they seldom would have reason to have these invasive recordings.

Here, we describe a case of a patient with remote bilateral arm amputations, who subsequently developed essential tremor. He elected to proceed with a DBS procedure, which was done with microelectrode guidance. We show that there is a large region of his thalamic ventral intermediate (Vim) nucleus that comprises neurons that are active during shoulder protraction, the movement he uses to open his prosthetic “hands.” We suggest that this reflects reorganization of this motor region of his thalamus.

Case Report

A 73-year-old, otherwise healthy male patient required bilateral forearm amputations in 1963 (age 19), after being electrocuted while working on a power line. His amputations were below the elbow, and he was fit with transradial prostheses with hook terminal devices. The hooks each included a pincer component held closed by an elastic band, and opened and manipulated via protraction of the ipsilateral shoulder. Prior to 2004, the patient was functionally independent, and could "pick up an ash from an ashtray" with his prostheses. Decades after his initial injury, he was refit with more advanced prostheses, but soon insisted on switching back to his hooks, so comfortable had he become with them.

In 2002, the patient developed a tremor in his lip. Within two years, he developed bilateral action and postural tremor primarily affecting his upper extremities. This progressed such that he could no longer use his prostheses to perform routine daily tasks. On the basis of his symptoms and family history, he was diagnosed with familial essential tremor. Interestingly, the patient had experienced phantom sensations for decades, but he had no somatosensory perception of his new onset tremor, and indeed did not appreciate his tremor with his eyes closed.

In 2015, the patient opted for bilateral deep brain stimulation (DBS) of the thalamic Vim nuclei. Six weeks following initial implantation, allowing time for any microthalamotomy effects to resolve, the patient underwent programming of his stimulator. This resulted in significant improvement in fine motor control, writing, utensil use, and drinking using his hook prostheses (Video 1). More than two years later, the patient continues to enjoy significant improvement in his quality of life and functional independence.

Methods

Implantation of DBS leads was performed (by RMB) on May 4 (left side) & 26 (right side), 2015, at the Halifax Infirmary (QEII Health Sciences Centre, Halifax, Canada). As part of

our usual procedure, the patient's head was fixed in a stereotactic frame for an MRI-guided stereotactic insertion of DBS leads (Medtronic 3387). An implantable pulse generator (Activa PC, Medtronic) was inserted following insertion of the second lead.

Our routine for DBS procedure involves the use of microelectrode recording to localise the targets for implantation. The Vim target was based on the AC-PC line and width of the third ventricle (Papavassiliou et al. 2008)). Using a 40μm exposed tip microelectrode (FHC, Bowdoin, ME), neurons were recorded, filtered (100Hz-5kHz), and digitized (20 kHz) using a GS3000 system (Molecular Devices, Sunnyvale, CA). Neuronal responses to a variety of voluntary movements were recorded while advancing the microelectrode through the Vim nucleus of the thalamus in a step-wise manner using an Alpha Omega microdrive (Nazareth, Israel), approximately 11mm lateral to the wall of the third ventricle.

The extracellular microelectrode recordings were imported into Spike 2 (CED, Cambridge, UK) for off-line analysis. Spikes were sorted using the software wave event template function to discriminate spikes based on a principal component analysis of spike properties including amplitude, shape, and duration (see Figure 2). For each recording, one to three unique spike templates were detected, allowing <2% variability in parameters. At each site, 6s periods were analysed (3s prior to and 3s following movement onset). For each individual neuron, we measured the instantaneous firing frequency and quantified the number of spikes in the pre-movement and movement conditions, and compared results using a paired Student's t-test.

Results

While it is usual to find that most responsive neurons in the Vim would increase their activity in response to digit, hand, and wrist movement, this was clearly not possible to test here given the patient's amputations. Surprisingly, we also did not find neurons that were active during volitional contralateral elbow movement. On the other hand, shoulder protraction, the

movement used to open the hook terminal devices of his prostheses, was associated with an increase in neuronal firing. Shoulder movements were not tested until late during the recording protocol on the left (first) side, likely because in our practice, it is unusual to find any shoulder movement-responsive neurons in Vim; we were initially focusing on elbow movements. However, a more systematic investigation was subsequently conducted on the right side, where we recorded shoulder movement-responsive neurons along a linear trajectory of over 5 mm (Figure 1). To quantify these changes, we were able to definitively identify nine neurons across this trajectory on the right side. Figure 1B illustrates 2 recordings at different locations, with the recording in Figure 1Ba resolved into three neurons in Figure 2. Each of the 9 identified neurons substantially increased their firing following movement initiation (Figure 3; p=0.0001). Thus, there was a surprisingly large length of the Vim comprising neurons associated with fine opening movements and manipulation of the prosthesis.

As we had not targeted the nucleus ventrocaudalis (Vc; equivalent to ventroposterior lateral and medial nuclei in non-human primates; see Figure 1A), we did not ask whether neurons in this region responded to tactile stimulation (receptive fields). However, as is our routine in practice, we did study projected fields by microstimulation (300Hz, 0.3 – 0.5ms, 5 – 25 μA stimuli) and found paresthesias involving the mouth region when stimulating the right thalamus, and top of the head when stimulating the left thalamus.

Discussion

We have had a rare opportunity to observe and report activity in a motor nucleus of the thalamus (Vim) in the context of amputation and long-term motor adaptation following remote bilateral upper extremity amputations. The territory of this patient's Vim that was activated during shoulder protraction – the movement used to control fine opening movements of his prosthetic 'hands' – was expanded in size compared to what we normally find in people with

intact limbs, suggesting that in this patient, there has been some use-dependent reorganization following amputation.

Vim is involved in motor coordination and is organised in a mediolateral somatotopic pattern (Lenz et al. 1990). It is roughly equivalent to the ventroposterolateral, pars oralis nucleus (VPLo) in non-human primates. This nucleus receives afferent kinesthetic input from contralateral body parts, and responds to active and passive muscle stretch (Ohye et al. 1989). Neurons in Vim receive direct excitatory input from deep cerebellar nuclei and cerebral cortex, as well as inhibitory input from the thalamic reticular nucleus. Output from Vim is primarily to cortical motor areas (Perlmutter and Mink 2006). Movement-related neurons in Vim increase their firing rate at movement onset of their corresponding body parts, and are typically recorded during microelectrode guided stereotactic Vim DBS surgery for tremor (Garonzik et al. 2002).

Plasticity of both Vim and the sensory ventrocaudalis (Vc; equivalent to ventroposterior lateral and medial nuclei in non-human primates) nucleus has been demonstrated in patients with tremor. In these patients, there is an expansion of the kinaesthetic representation of wrist and elbow movements, possibly resulting from chronic increases in afferent input (Kiss et al. 2003).

Little is known about reorganization of nuclei of the motor thalamus following limb amputation and adaptive recovery. Amputation-related plasticity has, however, been well documented in human somatosensory cortex, sensory thalamus, and motor cortex. Early animal studies demonstrated that peripheral median nerve transections in owl and squirrel monkeys leads to expansion of neighbouring ulnar and radial innervated skin representation into deafferented regions of somatosensory cortex (Kaas et al. 1983). Similar findings have been reported in humans (eg. Chen et al. 2002). In patients with limb amputations undergoing DBS surgery for pain, evidence for reorganization of sensory representations within Vc has been documented

via single linear microelectrode trajectories (Schmid et al. 2016). Stump tactile receptive fields within Vc are significantly enlarged after amputation, likely reflecting an expansion of stump representation into deafferented regions of the sensory thalamus (Davis et al. 1998).

Motor regions are also plastic. Following focal, sub-total lesions of the dorsal forelimb (DFL) area of rat primary motor cortex, the remaining DFL area can be either reduced or enlarged after recovery depending on whether the animals receive rehabilitative training (Nudo 2013). Limb amputation has been associated with reorganization of proximal muscle representations of the primary motor cortex in humans (Cohen et al. 1991). It is plausible that there would be corresponding plastic changes in the motor nuclei of the thalamus as well. Here we demonstrate that in Vim, many shoulder movement-responsive cells can be seen over a length of at least 5mm, in contrast with recordings in our usual practice, in which shoulder-movement responsive neurons are rarely recorded in this nucleus. We therefore conclude that the patient has had reorganization of his Vim nucleus.

The mechanisms underlying plasticity in Vim are not clear, and are likely multifactorial. In sensory thalamus, limb amputation leads to an increased number of bursting neurons in Vc (Lenz et al. 1998). While the mechanism of these changes is not clear, it was suggested that this pattern of spiking results from an activity-dependent increase in dendritic calcium spiking (Lenz et al. 1998). While decreased kinesthetic input from the distal arms following amputation could lead to similar changes in Vim, the fact that the activity was related to the movements that the patient developed to finely control his prostheses suggests that there is also a degree of use-dependent specificity to these changes.

It is possible that these types of changes following amputation lead to plasticity within Vim, with two driving influences: i) decreased afferent input to thalamic regions previously associated with

forearm, wrist, and hand movements, and ii) increased excitatory input from cerebellar and cortical areas associated with shoulder movements, secondary to the learning effects of using these movements for fine motor control. The combination of these mechanisms may have led to shoulder representation in regions formerly dedicated to distal arm fine motor control.

These observations took place in the context of routine electrode placement for DBS. As such, the patient did not have concurrent EMG recordings to correlate with Vim neuronal firing frequencies, nor were multiple repeated trials completed at any given electrode position. However, we have not previously encountered this extent of robust shoulder movement-responsive neurons. It is likely that a strong indication for invasive recording in motor thalamic nuclei of patients with remote amputations or other deafferenting injuries will remain a relatively rare opportunity. We are therefore presenting these findings to perhaps offer insights into the spectrum of neuroplastic changes that accompany amputation and adaptation.

Acknowledgements:

The authors would like to thank Carolyn Kelly, Christine Potvin, and Dr Heather Rigby for providing video and valuable feedback for this manuscript.

Disclosures: None

Funding:

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. *Neuroscience* 111: 761-773, 2002. doi:10.1016/S0306-4522(02)00025-8.

Cohen LG, Bandinelli S, Findley TW, Hallett M. Motor reorganization after upper limb amputation in man. A study with focal magnetic stimulation. *Brain* 114: 615-627, 1991. doi:10.1093/brain/114.1.615.

Davis KD, Kiss ZH, Luo L, Tasker RR, Lozano AM, Dostrovsky JO. Phantom sensations generated by thalamic microstimulation. *Nature* 391: 385-387, 1998. doi:10.1038/34905.

Dimyan MA, Cohen LG. Neuroplasticity in the context of motor rehabilitation after stroke. *Nat Rev Neurol* 7: 76-85, 2011. doi:10.1038/nrneurol.2010.200.

Garonzik IM, Hua SE, Ohara S, Lenz FA. Intraoperative microelectrode and semi-microelectrode recording during the physiological localization of the thalamic nucleus ventral intermediate. *Mov Disord* 17: S135-144, 2002. doi:10.1002/mds.10155.

Kaas JH, Merzenich MM, Killackey HP. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. *Annu Rev Neurosci* 6: 325-356, 1983. doi:10.1146/annurev.ne.06.030183.001545.

Kiss ZH, Davis KD, Tasker RR, Lozano AM, Hu B, Dostrovsky JO. Kinaesthetic neurons in thalamus of humans with and without tremor. *Exp Brain Res* 150: 85-94, 2003. doi:10.1007/s00221-003-1399-3.

Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR, Murphy JT, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Activity correlated with movement. *Brain* 113: 1795-1821, 1990. doi:10.1093/brain/113.6.1795.

Lenz FA, Garonzik IM, Zirh TA, Dougherty PM. Neuronal activity in the region of the thalamic principal sensory nucleus (ventralis caudalis) in patients with pain following amputations. *Neuroscience* 86: 1065-1081, 1998.

Nudo RJ. Recovery after brain injury: mechanisms and principles. *Frontiers in human neuroscience* 7: 887, 2013. doi:10.3389/fnhum.2013.00887.

Ohye C, Shibazaki T, Hirai T, Wada H, Hirato M, Kawashima Y. Further physiological observations on the ventralis intermedius neurons in the human thalamus. *Journal of neurophysiology* 61: 488-500, 1989. doi:10.1152/jn.1989.61.3.488.

Papavassiliou E, Rau G, Heath S, Abosch A, Barbaro NM, Larson PS, Lamborn K, Starr PA. Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. *Neurosurgery* 62 Suppl 2: 884-894, 2008. doi:10.1227/01.neu.0000316290.83360.7e.

Perlmutter JS, Mink JW. Deep brain stimulation. *Annu Rev Neurosci* 29: 229-257, 2006. doi:10.1146/annurev.neuro.29.051605.112824.

Rasmusson D. Changes in the organization of the ventroposterior lateral thalamic nucleus after digit removal in adult raccoon. *J Comp Neurol* 364: 92-103, 1996. doi:10.1002/(SICI)1096-9861(19960101)364:1<92::AID-CNE8>3.0.CO;2-N.

Schmid AC, Chien JH, Greenspan JD, Garonzik I, Weiss N, Ohara S, Lenz FA. Neuronal responses to tactile stimuli and tactile sensations evoked by microstimulation in the human thalamic principal somatic sensory nucleus (ventral caudal). *J Neurophysiol* 115: 2421-2433, 2016. doi:10.1152/jn.00611.2015.

Schaltenbrand G, and Wahren W. *Atlas for Stereotaxy of the Human Brain*. Stuttgart: Thieme, 1977.

FIGURE LEGENDS

Video 1: Patient performing various motor tasks using his transradial prostheses, first with the bilateral simulators 'off', and then with the stimulators 'on'. The patient has provided signed informed consent to be video-taped for publication.

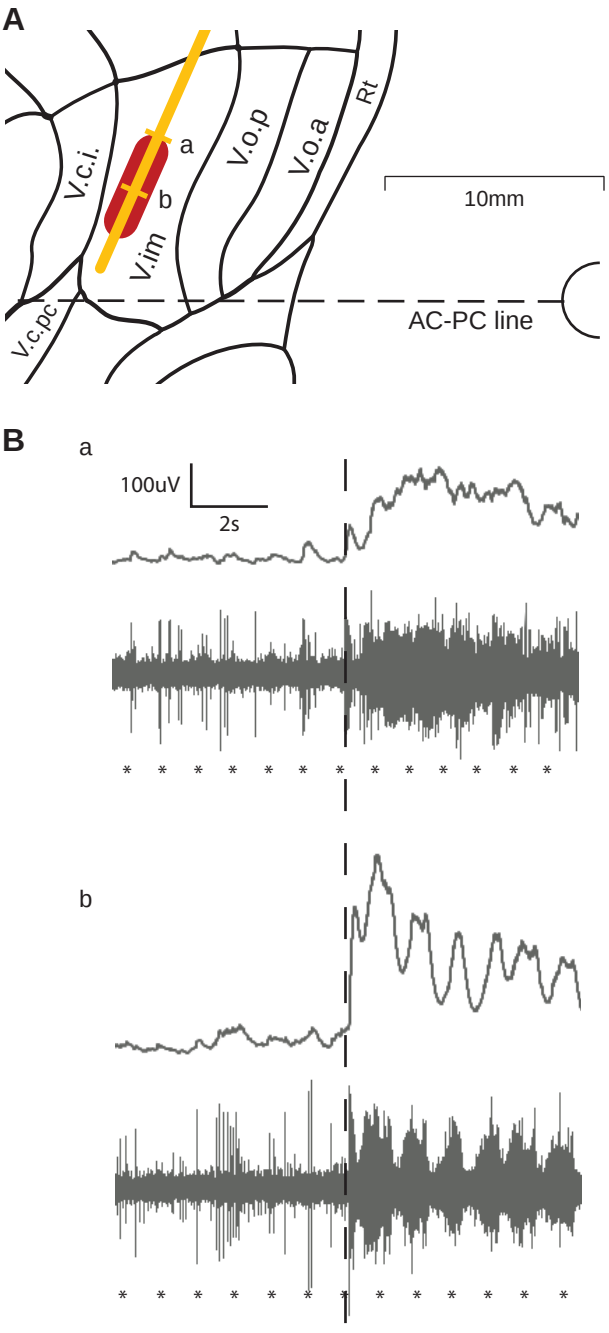
Figure 1: Microelectrode recording in the right thalamus during stimulator lead placement. Shoulder protraction led to an increase in Vim neuronal firing rates at each recording site over a trajectory length of over 5mm.

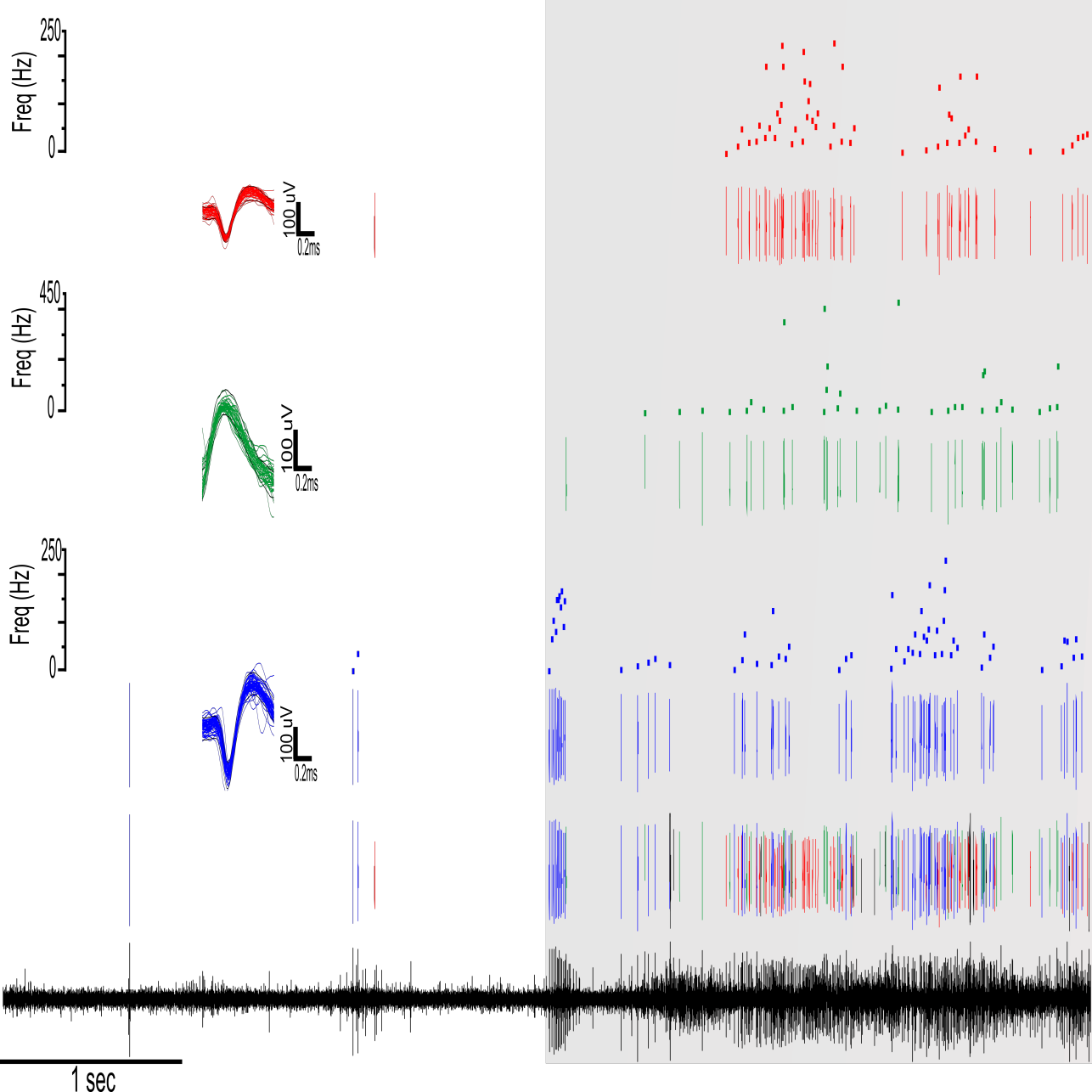
A: Track of the recording microelectrode through the right thalamus. This atlas image was stretched to match the patient's intercommissural distance, and the microelectrode track plotted (yellow line) based on initial target and angle of approach, and corroborated by position of DBS lead by overlaying with the post-operative MRI. The horizontal dashed line represents the AC-PC line. The red shaded area represents the linear extent of the microelectrode track over which neurons active during shoulder protraction were recorded. 'a' and 'b' denote recording sites depicted in panel B. V.c.i: ventral caudal internal nucleus, V.c.pc: ventral caudal parvocellular nucleus, V.im: ventral intermediate nucleus, V.o.p: ventral oral posterior nucleus, V.o.a: ventral oral anterior nucleus, Rt: reticular nucleus. Adapted from Schaltenbrand & Wahren (1977), Plate 44, 13mm right of midline.

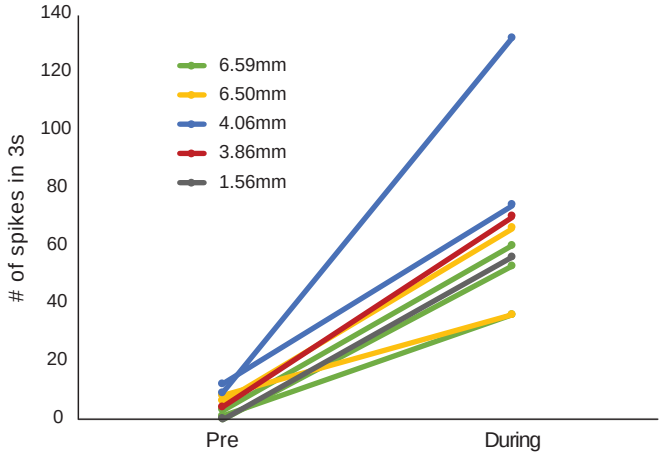
B: Microelectrode recordings from sites indicated in panel A. Recording locations above target are a: 6.59mm; b: 3.86mm. The lower traces are raw recordings. The upper traces have been rectified and integrated. The vertical dashed line indicates the approximate time of onset of shoulder protraction.

Figure 2: Individual neurons increase their firing rate following movement onset. Microelectrode recording at 6.59mm above target on the right side, showing the raw extracellular microelectrode recording (bottom, black trace), and 3 discriminated neurons (blue, green, and red). Spikes were identified (insets) and analysed for a period of 3s before and 3s after onset of shoulder protraction. The instantaneous spike frequency relative to the previous spike is plotted above each sorted spike. The shaded area to the right of the figure represents the period following onset of left shoulder protraction.

Figure 3: Neurons over a length > 5mm increased their firing rates following movement onset. Total number of spikes before (3s) and after (3s) onset of shoulder protraction in 9 neurons at 5 microelectrode sites. The spike count was significantly greater after movement onset, (p=0.0001).


A
V.c.i.
a
b
V.o.p
V.o.a
Rt
V.im
10mm
V.c.pc
AC-PC line
B
a
100uV
2s
b


Freq (Hz)
250
0
100 uV
0.2ms
Freq (Hz)
450
0
100 uV
0.2ms
Freq (Hz)
250
0
100 uV
0.2ms
1 sec


140
120
100
80
60
40
20
0
# of spikes in 3s
6.59mm
6.50mm
4.06mm
3.86mm
1.56mm
Pre
During