Differences in Neuronal Firing Rates in Pallidal and Cerebellar Receiving Areas of Thalamus in Patients With Parkinson’s Disease, Essential Tremor, and Pain

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Submitted 25 August 2004; accepted in final form 4 February 2005

Molnar, G. F., A. Pilliar, A. M. Lozano, and J. O. Dostrovsky. Differences in neuronal firing rates in pallidal and cerebellar receiving areas of thalamus in patients with Parkinson’s disease, essential tremor, and pain. J Neurophysiol 93: 3094–3101, 2005. First published February 9, 2005; doi:10.1152/jn.00881.2004. The motor symptoms of Parkinson’s disease (PD) are thought to result from increased inhibitory outflow from the basal ganglia to the pallidal receiving areas of thalamus (ventral oral anterior and posterior—Voa, Vop). To test this hypothesis, we examined the firing rates of neurons in pallidal and cerebellar receiving areas of thalamus in five PD patients and compared them to those of neurons in comparable regions of motor thalamus in two other patient groups where hyperactivity of GPe is not believed to occur [essential tremor (ET), pain]. Neuronal recordings were made during microelectrode-guided functional stereotactic neurosurgery. The mean spontaneous firing rate (MSFR) of neurons classified as voluntary neurons and presumed to be in the pallidal receiving areas of thalamus in PD patients [7.4 ± 1.0 (SE) Hz] was significantly lower (P < 0.01) than in the ET (18.1 ± 3.0 Hz) and pain (19.0 ± 1.9 Hz) groups. In contrast, the MSFR of neurons classified as kinesthetic and presumed to be primarily in the cerebellar receiving area of thalamus (ventral intermediate—Vim), although some are probably in the deep shell region of the ventrocaudal nucleus (VPLa), was significantly greater in ET patients (25.8 ± 3.5 Hz) than in the PD (14.3 ± 1.6 Hz; P < 0.01) and pain (16.1 ± 1.5 Hz; P < 0.05) groups. Similar findings were obtained when the neurons were grouped according to their estimated locations in Voa/Vop and Vim of motor thalamus. These data provide support for the prediction of the classical pathophysiological model of PD and moreover suggest that pathophysiology in the cerebello-thalamo-cortical pathway may be a possible cause of tremor in ET patients.

INTRODUCTION

According to the now classic model of the pathophysiology of Parkinson’s disease (PD), the cardinal symptoms of akinesia and bradykinesia are believed to be due to hyperactivity of the basal ganglia output nuclei [i.e., globus pallidus internal (GPi) and substantia nigra pars reticulata, which leads to depression of thalamic neurons and motor cortical areas (Albin et al. 1989; DeLong 1990)]. An increase in GPi neuronal firing rates has been observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primates (Filion and Tremblay 1991; Heimer et al. 2002; Miller and DeLong 1987), and the firing rates in PD patients are similar to those in the parkinsonian MPTP-treated primates (Hutchison et al. 1994; Merello et al. 1999), suggesting that they are also elevated compared with normal. In accordance with the predictions of the model, lesions in GPi of PD patients improve parkinsonian symptoms (Lozano et al. 1995). Furthermore, administration of dopaminergic medication in MPTP monkeys and PD patients decreases GPi and increases GPe neuronal activity according to the predictions of the model (Filion et al. 1991; Heimer et al. 2002; Levy et al. 2001; Merello et al. 1999; Papa et al. 1999). Thus according to this model the firing rates of neurons in the pallidal receiving area of motor thalamus should be depressed in PD.

Essential tremor (ET) is a movement disorder generally characterized by monosymptomatic action or postural tremor with a frequency of 4–12 Hz (Findley and Koller 1987). The pathophysiology of ET is mostly unknown but not believed to be associated with significant basal ganglia dysfunction. The tremor in PD and ET can be effectively treated by thalamotomy or thalamic deep brain stimulation (DBS) in the ventral intermediate nucleus (Vim), the presumed thalamic cerebellar relay nucleus, at approximately identical locations (Benabid et al. 1996; Hassler 1959; Jankovic et al. 1995; Macchi and Jones 1997; Schulder et al. 1999; Shahzadi et al. 1995; Siegfried 1993; Tasker 1990). It is thus of interest to examine whether the firing rates of neurons in this region are comparable in these two disorders but different from normal.

Extracellular recordings obtained during thalamic exploration in human patients undergoing functional stereotactic surgery provide a unique opportunity to examine the firing rates of neurons in these two regions of thalamus in these two neurological conditions. The functional mapping of thalamus in patients undergoing surgery for relief of pain also entails recordings in these regions of thalamus and thus can provide a good approximation of a normal motor thalamus and can be used for comparison purposes.

Neurons in the motor thalamus that respond to voluntary movements are located largely within the ventral oral nucleus (Vo), which is generally subdivided into anterior and posterior subnuclei (Voa/Vop) (Hassler 1959; Krack et al. 2002; Lenz et al. 2002), and neurons that respond to kinesthetic/passive movements about a joint are primarily contained within Vim (Krack et al. 2002; Ohye et al. 1976; Raeva et al. 1999; Tasker and Kiss 1995). Voa/Vop areas of motor thalamus and equivalent areas in monkey thalamus [VLo (Olszewski 1952), VLa (Hirai and Jones 1989)] primarily receive input from the basal ganglia and project preferentially to premotor areas of cortex (Hirai and Jones 1989; Macchi and Jones 1997). Vim and the equivalent area in monkey [VPLo (Olszewski 1952), VLP...
(Hirai and Jones [1989]) motor thalamus primarily receives input from the cerebellum and projects to primary motor cortex (Krack et al. 2002; Macchi and Jones 1997).

The primary aim of the present study was to determine whether the spontaneous firing rates of neurons in Voa/Vop in PD patients is lower compared with the other two groups of patients examined. Two methods were used to identify Voa/Vop neurons—neurons classified as voluntary (see preceding text) or neurons located >2 mm anterior to the tactile border between Vim and the ventral caudal nucleus (Vc), which according to the stereotactic atlas of Schaltenbrand and Wharen (1977) is approximately the border of Vim and Vop.

The firing rates of the Voa/Vop neurons were also compared with the firing rates of neurons in Vim. Neurons were identified as being in Vim if they were classified as kinesthetic neurons or if they were located within 2 mm of the tactile border. Previous electrophysiological studies in humans have assumed that the kinesthetic neurons located anterior to the anterior tactile border of the sensory relay nucleus Vc are in Vim. Although it is generally accepted that Vc in the human only includes tactile stimulation-responsive neurons, on the basis of primate electrophysiological and anatomical studies and human anatomical studies (see Hirai and Jones 1993), there should be a layer or shell of kinesthetic cells lying immediately anterior to the tactile “core” of Vc, which receives leminiscal inputs and projects to areas 3a and 2 of primary somatosensory cortex. This shell region has been termed VPLa by Jones (see Hirai and Jones 1993; Jones 1997; Macchi and Jones 1997) and should be included as part of Vc. We have observed in some cases (unpublished observations) that there is a thin layer of neurons immediately anterior to the location of the neurons responding to tactile stimuli that have very low thresholds and robust responses to deep and/or small movements of digits or joints and likely corresponds to VPLa. Microstimulation in this region will usually produce parasthesia or occasionally sensations of movement or tightness at low intensities. However, it is usually not clear exactly where the border between this region, presumably VPLa, and Vim occurs and so some of the Ki cells in this study may have been located in VPLa rather than Vim. Therefore in this report we have termed this region Vim/VPLa to acknowledge this uncertainty. Some of the findings have been briefly reported previously (Dostrovsky et al. 2001).

Methods

Detailed descriptions of the techniques used in this study have been previously published and will only be discussed briefly here (Dostrovsky 1999; Lenz et al. 1988; Tasker et al. 1998). Data were obtained from patients with PD (n = 5, aged 67–73 yr), ET (n = 10, aged 64–75 yr), and chronic pain (pain; n = 5, aged 45–71 yr). The patients with ET had their symptoms for >5 yr, and conventional pharmacological treatment was not effective in relieving their tremor. The pain control group consisted of individuals with chronic pain disorders: anesthesia dolorosa (2), multiple sclerosis, spinal cord injury, and central pain due to head injury. MRI imaging of the latter two patients did not reveal any brain lesions and for the MS patient revealed only white matter lesions adjacent to the lateral ventricles. There were no imaging data available for the two anesthnesia dolorosa patients. The procedures were approved by the Human Experimentation Committee of the University of Toronto, and patients gave informed consent. All patients underwent similar stereotactic thalamic explorations to localize a surgical target. The coordinates of the initial electrode trajectory were based on imaging-based identification of the locations of the anterior and posterior commissures which were then used to obtain an appropriately scaled map of thalamus from the standard atlas maps of Schaltenbrand and Wharen (1977). Subsequent electrode tracks were guided by the physiological findings obtained from the first track.

Neuronal recordings were made along several parasagittal trajectories traversing Vop, Vim and Vc. Those trajectories which passed through the tactile representation of the hand (usually 15 mm lateral), were selected for the present study. Thalamic neurons were tested for responses to passive and active joint movements and cutaneous and deep stimulation. Active and passive movements of the arm and hand included shoulder, elbow, wrist, and digit movements as well as arm reaching and making a fist. Movement-related neurons were classified as voluntary if they responded only or primarily to active (i.e., voluntary) joint movements. Although some may also have a weak response to passive movements (i.e., by the experimenter), the response magnitude was always clearly much less than that due to a similar voluntary movement. Neurons that responded to passive movements equally or more intensely than to similar voluntary movements were classified as kinesthetic. Stimulation of the body surface by brushing or light stroking was used to identify cutaneous somatosensory-responsive neurons in the tactile relay nucleus, Vc.

Only well-isolated neurons that could be classified as voluntary or kinesthetic were analyzed. Single action potentials were discriminated with the aid of a dual window and time discriminator or a spike template matching program (Spike2, Cambridge Electronic Design, Cambridge, UK). Firing rate and firing pattern (see following text) were calculated for periods (usually ≥20 s) when the patient was at rest and no limb tremor or other movements occurred, usually after the characterization of the neuron. For assessing firing pattern, we used a simplified version of the burst analysis described by Kanoke and Vitek (1996). The spike train was expressed as discharge density by calculating the number of spikes in each successive interval equal to the reciprocal of the mean firing rate. The number of occurrences of intervals containing 0 spikes, 1 spike, 2 spikes etc. was determined and plotted as a histogram. This discharge density histogram represents the probability distribution of the neuron’s discharge density and was compared with a discharge density of a Poisson process with a mean of 1 by using a χ² goodness-of-fit test. When the discharge density distribution was statistically similar to a Poisson process, the neuron was classified as “random.” When the neuron’s discharge pattern was significantly nonrandom, then the firing pattern was classified as “regular” when the probability of finding one spike per time segment was high or “irregular” when the probability of finding no spikes or many spikes per time segment was high (see Levy et al. 2001 for further details). Although convenient and widely used this categorization does not provide any further insights into the types of patterns or bursts that lead to the irregular pattern.

Thalamic cells are also well known to fire in characteristic bursts due to low-threshold calcium spikes under some conditions (e.g., sleep) (Radhakrishnan et al. 1999; Sherman and Guillery 2001; Tsukatos et al. 1997). These can be easily identified by an examination of their characteristic intraburst firing pattern. All of the cells analyzed in this study as well as all other cells encountered in the electrode tracks were qualitatively assessed for such bursting activity on the basis of auditory and visual scrutiny of the raw recordings at the time of the recordings in the OR.

The stereotactic locations of the recorded neurons normalized to the standard atlas AC-PC length at a sagittal plane of 14.5 mm from the midline were determined. The electrode track positions were adjusted in the AC-PC axis so that the location of the first tactile responsive cell, signifying entry into the Vc nucleus, was on the border between Vim and Vc. The locations were plotted relative to the AC-PC line (abscissa) and a line perpendicular to the AC-PC line at the location of the first tactile neuron in that same trajectory (ordinate) (i.e., anterior Vc border). This was done because the tactile border within Vc is a well-defined physiological landmark, whereas the border
between the presumed deep shell of Vc (VPLa) is not easily determined. The difference in mean anterior-posterior locations of Vol and Ki neurons was compared for each patient group [1-way ANOVA with Newman-Keuls multiple comparison post hoc test (α = 0.05)]. Mean spontaneous firing rates of neurons within or beyond 2 mm of the Vc border were also compared for each patient group; 2 mm is the approximate width of Vim based on anatomy (Hassler 1959; Schaltenbrand and Wahren 1977) and physiological recordings by our group. This serves as a second method for differentiating neurons in Vim/VPLa versus Voa/Vop. Voluntary-responsive neurons and neurons located >2 mm anterior to the Vc border were presumed to be located in the Voa/Vop region and kinesthetic-responsive neurons and those located <2 mm anterior to the Vc border were presumed to be located in Vim/VPLa.

The mean firing rates for neurons in each of the three groups of patients [grouped either by physiological properties—Vol and Ki or by location (>2 mm or <2 mm from tactile border)—were calculated. These data were statistically analyzed within and between patient groups using a one-way ANOVA and Newman-Keuls multiple comparison post hoc test, with a level of significance of α = 0.05. A comparison of the three types of firing patterns by the six patient/nucleus groups was performed using χ² analysis with the null hypothesis that the proportions were the same.

RESULTS

A total of 118 neurons was analyzed in the 20 patients. Of these 61 were classified as Vol and the remainder as Ki.

Firing rates of neurons

Vol Neurons. The MSFR of Vol neurons was markedly lower in PD patients (7.4 ± 1.0 Hz) than in the other two groups of patients and this difference was statistically significant (P < 0.01; see Fig. 1A). The MSFR of neurons located >2 mm in front of Vc in PD patients was also found to be lower in comparison with the other 2 groups and was statistically significant (P < 0.01; see Fig. 1B).

Ki Neurons. The MSFR of Ki neurons in ET patients was significantly greater than in pain patients (P < 0.05), and in PD patients (P < 0.01; see Fig. 1A). The same findings were obtained when the neurons were grouped according to location anterior to Vc. The MSFR of neurons in this <2 mm zone in ET patients was significantly greater than in pain patients (P < 0.001), and in PD patients (P < 0.001; see Fig. 1B).

Plots of the anterior-posterior location of neurons and their corresponding MSFR for each patient group (not shown) clearly show a marked decrease in MSFRs for neurons located >2 mm from the Vc border in the PD and ET patients. These trends are consistent with the results presented in Fig. 1A and B.

Firing patterns of neurons

Neuronal firing patterns were determined using a method based on the Kaneoke and Vitek method. As such neurons were classified as either irregular/bursting, random, or regular. The proportion of these neuronal types found within the Voa/Vop and Vim/VPLa nuclei of the three patient groups is shown in Fig. 2. A comparison of the three neuronal types by the six patient/nucleus groups was performed using chi squared analysis. We found a significant χ² value (109, df = 10, P < 0.0001), indicating that the proportions of neuronal types were not the same across the six groups. Post hoc analysis of cell contributions revealed that in the Voa/Vop region in PD patients there was a significantly lower proportion of regularly firing neurons, and that within the Vim/VPLa of ET patients, there was a significantly higher proportion of irregularly firing neurons.

None of the neurons studied in any of the groups fired in the characteristic bursting pattern that results from low-threshold calcium spikes. Furthermore, recordings from other neurons (not movement responsive) in these electrode trajectories yielded very few neurons firing in bursts of the calcium spike type and there was no difference in incidence of these in PD patients compared with the ET patients (P > 0.05).

Locations of Vol and Ki neurons

The stereotactic locations of the neurons in the anterior-posterior axis were analyzed. For all three patient groups, the mean location of Vol neurons was significantly more anterior than the mean anterior-posterior location of Ki neurons (P < 0.001; Fig. 3). Based on the predicted thalamic anatomy, the mean location of Vol neurons for all three patient groups was within Voa/Vop and the mean location of Ki neurons was within Vim/VPLa.

DISCUSSION

Firing rates in Vo in PD patients

The major finding of this study was that the MSFR of movement-related neurons in Voa/Vop in PD patients was significantly lower than those of similar neurons in the other two groups of patients (see Fig. 1). These results are consistent with findings of lower mean spontaneous firing rates (11.5 vs. 16 Hz) and increased bursting in monkey VLo (the human equivalent of Voa/Vop) in MPTP-treated versus normal animals (Vitek et al. 1994b). The firing rate in Vo that we observed in this study for pain patients is comparable to the 17-Hz rate (mean interspike interval of 59 ms) reported by Lenz et al. (1999) in pain patients at rest. Although it is possible that one or more of the pain patients in our "control" group had some minor damage to the basal ganglia we view this as unlikely because the imaging in the two trauma patients did not reveal abnormalities and the two anesthesia dolorosa patients developed pain due to tumors that did not affect the thalamus or basal ganglia.

The decreased firing rates we observed in Vo in PD patients are consistent with the predictions of the Albin/DeLong basal ganglia model because the hyperactivity in GPi should lead to decreased firing rates in the pallidal receiving area of thalamus. Induction of parkinsonism in monkeys with MPTP has generally been shown to result in an increase in GPi firing rates (Filion and Tremblay 1991; Heimer et al. 2002; Miller and DeLong 1987) and the GPi firing rates in PD patients are similar to those in the MPTP-treated primates (Hutchison et al. 1994; Merello et al. 1999), suggesting that they are elevated compared with normal. Thus it is reasonable to assume that the firing rates of the neurons in GPi of the PD patients in our study were elevated in comparison to those in the other two patient groups where there is no reason to suspect alterations in pallidal firing rates from normal.

The low firing rates in Vo observed in this study would be expected to reduce the firing rates and excitability of premotor neurons.
Thus the findings are also consistent with decreased activity of supplementary motor area (SMA) of the cortex, a major projection target of the neurons in Vo (Macchi and Jones 1997) that has been reported in functional imaging studies in PD patients (Jenkins et al. 1992; Limousin et al. 1997). However, recent studies in MPTP-treated monkeys have failed to find a significant increase in GPi firing rates (Boraud et al. 1998; Raz et al. 2000; Wichmann et al. 1999). Furthermore, recent studies have provided evidence that deep brain stimulation, which alleviates the symptoms of PD and which is assumed to act by inhibiting the firing in GPi, may actually be exciting the neurons that according to the model should exacerbate the parkinsonian symptoms (Anderson et al. 2003; Hashimoto et al. 2003; Windels et al. 2000). Thus it is possible that the firing rates of GPi neurons in PD are not elevated, in which case there must be some other cause for the depressed Vo firing rates we observed.

**Firing patterns**

It is interesting that the only significant differences in firing patterns were observed for the two groups where significant changes in firing rate were also observed. This suggests that...
pathophysiological changes in PD and ET that resulted in changes in firing rates also changed the firing patterns. Unfortunately these findings do not provide any direct insights into the underlying mechanisms causing these changes or their functional implication.

If Gpi is hyperactive in PD, then this could lead to pronounced hyperpolarization of neurons in the pallidal receiving areas of thalamus and could cause them to switch to the burst mode of firing. It has been suggested that the low-threshold calcium spike (LTS) low-frequency oscillatory bursting activity characteristic of this firing mode may give rise to the motor symptoms of PD (Llinas et al. 1999). However, none of the Ki or Vol neurons analyzed for this study fired in LTS bursts and the incidence of the small number of other neurons firing in LTS bursts observed during the recordings in the PD patients was not significantly different from that observed in similar trajectories through Vop in the ET patients. Thus LTS bursting does not appear to be a likely mechanism underlying PD symptoms, at least in the part of thalamus explored in these studies.

Firing rates in Vim/VPLa in ET patients

Also of considerable interest was the finding that the MSFR of neurons in the cerebellar receiving area of thalamus (Vim) in ET patients was significantly greater than in pain and PD patients (see Fig. 1). Our “control” values for MSFRs in pain patients of 16Hz are fairly similar to the values of 13 and 14 reported recently in two studies by Lenz et al. (1999, 2002). However, in the monkey, Vitek et al. (1994b) reported that the MSFR in Vim (VPLo) was considerably higher (22 Hz). Interestingly, however, they reported that this MSFR drops to 15 in MPTP-treated monkeys which is the same as the 15 Hz we found in the PD patients. This raises the possibility that Vim/VPLa firing rates are lower than normal in both PD and pain patients. Nevertheless, the MSFRs we have observed in the ET patients are slightly elevated compared with the MSFRs in normal monkeys and compared with the values reported by Lenz et al. (2002) in their control group, which included both pain and PD patients. Interestingly, they found a much lower MSFR for Vim/VPLa neurons in patients in their intention tremor group, which comprised cerebellar-damage and MS-tremor patients. The higher MSFRs we observed in the ET patients were not caused by the patients’ tremor because the firing rates were determined for periods at rest when the neurons were not excited by tremor-related movements of the joints. They were thus in a comparable state to that in the PD and pain patients who also did not have tremor or limb movements during the periods used to determine the MSFRs.

Animal studies suggest that the olivocerebellar circuit may be involved in tremor generation (Lamarré 1984; Lamarré et al. 1971; Llinás and Volkind 1973). Furthermore, recent evidence from human studies suggests that the cerebellothalamocortical pathway is involved in the pathophysiology of ET. Functional imaging data from ET patients during involuntary tremor and also at rest without tremor has shown increased bilateral cerebellar activation and deep cerebellar nuclei activation (Bucher et al. 1997; Jenkins et al. 1993; Wills et al. 1994). Overactivity from the cerebellum in ET should increase the activity in Vim (Macchi and Jones 1997). Bucher and colleagues using functional magnetic resonance imaging (fMRI) found overactivation (increased blood flow) in the contralateral thalamus in ET patients during tremor (Bucher et al. 1997). Tremor cells are commonly found in Vim/VPLa in ET patients and lesions made in areas of tremor cells can abolish tremor (Brodkey et al. 2004; Goldman et al. 1992; Jankovic et al. 1995). Thus it is possible that in ET there is cerebellar hyperactivity that leads to increased firing of Vim neurons. We
propose that the increase in MSFR of Ki neurons found in our ET patients is pathological and predisposes the system to oscillation along the olivocerebellothalamic pathway giving rise to tremor.

Locations of recorded neurons

The results of our analysis with respect to the locations of the neurons showed a good match between the physiology and anatomic location of thalamic neurons. For all three patient groups, the mean location of Vol neurons was significantly more anterior than the mean anterior-posterior location of Ki neurons (P < 0.001; Fig. 3) and corresponded with the predicted locations within Vo and Vim/VPLa, respectively. Similarly, the MSFR of Vol and Ki neurons was similar to the MSFR of neurons grouped according to predicted anatomic location within Vo and Vim/VPLa. Thus categorizing “voluntary-responsive” neurons as Voa/Vop neurons and “kinesthetic-responsive” neurons as Vim/VPLa neurons were not unreasonable assumptions. It is also of interest to note that there was some overlap of Ki and Vol neurons especially near the Vop Vim border. This is not surprising in view of anatomical and electrophysiological studies in monkey thalamus (Percheron et al. 1996; Sakai et al. 2000; Vitek et al. 1994a) showing that there is substantial interdigitation of the two regions near their boundary. Our conclusions regarding the predictions of Albin/DeLong rate model depend on the assumption that neurons in Vop/Voa are in the pallidal receiving area of motor thalamus. Although most authors agree with this assumption (Hirai and Jones 1989; Krack et al. 2002; Lenz et al. 2002), some studies have suggested that at least part if not all of Vop receives cerebellar rather than pallidal input (see Krack et al. 2002).

In summary, this study has shown that the firing rates of neurons in Voa/Vop, which are presumed to be largely in the pallidal receiving area of thalamus, are lower in PD than in ET and pain patients. This is consistent with the predictions of the Albin/DeLong rate model of basal ganglia function. We also found increased firing rates of neurons in Vim/VPLa of patients with ET, suggesting that the increased activity may be related to the pathology and provide a possible explanation for the effectiveness of Vim lesions and DBS in treating ET. This latter suggestion is not at variance with the fact that DBS or lesions in Vim are also effective in treating parkinsonian tremor. There are likely to be several different mechanisms that can give rise to tremor, and yet they can share some common features and circuits. The oscillatory tremor-related activity in the Vim that occurs during both PD and ET tremor and that is relayed to motor cortex is likely to be an important common component of the tremor generating network in both conditions even though the alterations in other parts of the network necessary for generating the tremor are different. Such oscillatory activity would be disrupted by DBS and lesions in Vim. Furthermore or alternatively, in both cases, these interventions will also alter motor cortex activity and motor cortex is likely to be involved in mediating both types of tremor. In addition, the effects of stimulation and lesions may not be entirely limited to Vim, and spread into Vop or VPLa could possibly mediate some of the beneficial therapeutic effects in PD patients.

GRANTS

This work was supported by grants from The Parkinson Foundation of Canada, Canadian Institutes of Health Research and National Institutes of Health to J. O. Dostrovsky and by Brain Injury Community Re-Entry (Niagara) Inc. and Ontario Graduate Scholarship and Ontario Graduate Scholarship in Science and Technology to G. F. Molnar.


