ORIGINAL ARTICLE

The Association of Dexmedetomidine with Firing Properties in Pallidal Neurons

Majid Gasim, Suneil K. Kalia, Mojgan Hodaie, Andres M. Lozano, Lakshmikumar Venkatraghavan, William D. Hutchison

Abstract: ***Background:*** Microelectrode recordings (MERs) are used during deep brain stimulation surgery (DBS) to optimize patient outcomes and provide a unique method of collecting data regarding neurological conditions. However, MERs can be affected by anesthetics such as dexmedetomidine. Little is known about the effects of dexmedetomidine (DEX) on the globus pallidus interna (GPi), a common target for DBS. The primary aim of this study is to investigate the hypothesis that DEX is associated with alterations in GPi MERs. ***Methods:*** We conducted a retrospective analysis comparing MERs from patients with Parkinson's disease (PD) and dystonia who underwent insertion of DBS of the GPi under DEX sedation with those who went through the same procedure without DEX (No DEX). ***Results:*** Firing rates for GPi neurons in the DEX group were lower (57.44 ± 2.04; mean ± SEM, n = 163 cells) than the No DEX group (69.53 ± 2.06, n = 112 cells, P < 0.0001). Overall, DEX was associated with a greater proportion of GPi cells classified as firing in bursty pattern compared to our No DEX group. (29.41%, n = 153 vs 14.81%, n = 108, P = 0.008). This effect was present for both PD and dystonia patients who underwent the procedure. High doses of DEX were associated with lower firing rates than low doses. ***Conclusions:*** Our results suggest that DEX is associated with a decrease in GPi firing rates and are associated with an increase in burstiness. Furthermore, these effects are similar between dystonia and PD patients. Lastly, the effects of DEX may differ between high doses and low doses.

RÉSUMÉ : La dexmédétomidine et les propriétés de décharge électrique des neurones du pallidum. ***Contexte :*** Les enregistrements par microélectrodes (EME) s'utilisent durant les interventions chirurgicales de stimulation cérébrale profonde (SCP) afin d'optimiser les résultats, et ils constituent un moyen unique en leur genre de collecte de données sur les troubles neurologiques. Toutefois, les EME peuvent être modifiés par les anesthésiques, par exemple la dexmédétomidine. On connaît peu de choses sur les effets de la dexmédétomidine sur le pallidum interne (PI), cible courante de la SCP. L'étude dont il est question ici avait pour objectif principal d'examiner l'hypothèse selon laquelle la dexmédétomidine est associée à une altération des EME dans le PI. ***Méthode :*** L'équipe a procédé à une analyse rétrospective, visant à comparer les EME effectués chez des patients souffrant de la maladie de Parkinson (MP) ou de dystonie qui ont subi une intervention de SCP du PI sous sédation par la dexmédétomidine (groupe avec DEX) avec ceux obtenus chez des patients ayant subi le même type d'intervention mais sous sédation par un autre anesthésique (groupe sans DEX). ***Résultats :*** Le taux de décharge des neurones du PI dans le groupe de dexmédétomidine était inférieur (57,44 ± 2,04; moyenne ± erreur-type; n = 163 cellules) à celui enregistré dans le groupe sans DEX (69,53 ± 2,06; n = 112 cellules; P < 0,0001). Dans l'ensemble, la dexmédétomidine a été associée à une proportion plus grande de cellules du PI classées dans la catégorie des décharges en salve que les autres anesthésiques (groupe sans DEX) (29,41 %; n = 153 contre 14,81 %; n = 108; P = 0,008). L'effet a été observé autant chez les patients souffrant de MP que chez ceux souffrant de dystonie qui ont subi ce type d'intervention. Les doses élevées de dexmédétomidine ont été associées à un taux plus bas de décharge que les faibles doses. ***Conclusion :*** Les résultats donnent à penser que la dexmédétomidine est associée à une diminution du taux de décharge dans le PI mais à une augmentation des décharges sous forme de salve. En outre, ces effets sont similaires chez les patients atteints de dystonie ou de MP. Finalement, les effets de la dexmédétomidine peuvent différer selon les doses administrées : faibles ou fortes.

Keywords: Microelectrode recordings, Dystonia, Parkinson's disease, GPi, Deep brain stimulation, Dexmedetomidine

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Introduction

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) is an established treatment for movement disorders such as Parkinson's disease and dystonia.[1–4] DBS involves the surgical placement of electrodes into the patient's brain to stimulate and thereby "correct" the pathological neuronal activity which may be responsible for some of the symptoms of the movement disorder.

In order to optimize clinical benefit, final placement of the DBS electrode needs to be as precise as possible.[5] Microelectrode recordings (MERs) are used intraoperatively to confirm the localization of the target nuclei and provide an unparalleled opportunity to study the pathologies underlying these disorders as they occur in humans.[6] Unfortunately, anesthetic agents can interfere with the procurement of MERs by altering the

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neurophysiological properties of different nuclei, including the GPi and subthalamic nucleus (STN).[7–10] While the majority of these studies have focused on the STN, fewer studies have investigated the effect on the GPi. The GPi is often the DBS target chosen for patients with dystonia or dystonia dominant PD, and provides a more challenging case for the anesthesiologist, often requiring more sedation. This may interfere with the strategic utility of MERs, or may lead to misinterpretations of the relationships between MERs and the movement disorders in question. Thus, it is useful to understand the impact of MERs on target nuclei.

Dexmedetomidine (DEX) is an agonist of the alpha-2 adrenergic receptor, and has been widely used for conscious sedation during neurosurgical procedures.[5] It produces mild sedative, anxiolytic, hypnotic, and analgesic effects without many of the side effects of other sedative agents such as respiratory depression and cognitive impairment.[5,11]

DEX possesses favorable properties as an anesthetic agent, previous reports have shown that DEX alters the firing properties of STN neurons in patients with PD, leading to increased firing rates and decreased burstiness.[7,8] However, we do not know how DEX affects the neuronal properties of the GPi and whether this depends on disease pathology. Unlike the STN, the GPi does not receive substantial noradrenergic innervation from the Locus Coeruleus.[12,13] The effects of DEX on GPi neurons could be mediated indirectly through the inhibition of brain regions innervated by the Locus Coeruleus, such as the striatum, STN, or cortex. The primary aim of this study is to investigate the *a priori* hypothesis that DEX will alter MERs of the GPi, and the secondary aim is to investigate differences in MERs between PD and dystonia patients.

Methods

Patients

After the institutional research ethics board approval (#14-7506-BE), we retrospectively analyzed the MERs obtained from patients who underwent DBS electrode placement in the GPi for PD or dystonia, under DEX sedation. Informed consent was obtained from all patients in compliance with the guidelines of the research ethics board. Study design and analysis was performed in conjunction with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14] Patients were identified through the review of medical records from January 1, 2014 to May 1, 2017. Patients were included if they: (1) underwent DBS of the GPi for PD or dystonia, (2) had intraoperative MER for target localization, for which data was available, and (3) received either DEX or no sedation (No DEX) with local anesthetic for the procedure. Patients were included in the "no sedation" group only if they had not received any systemic administration of anesthetic agents for the duration of the procedure, but still received local anesthetic for frame pin points and surgical incisions. Due to limitations in available data, study size was determined by including all eligible participants. Data collected included patient demographics, MER, anesthetic management, and indication for DBS. We did not register our study on a clinical trials registry due to its retrospective nature.

Anesthesia Management

All patients were assessed by an anesthesiologist in the preoperative anesthesia consult clinic, prior to the procedure. Twelve hours prior to the planned start time of the procedure, all patients were asked to withhold their medication. Any dopamine agonists were tapered off the week prior under neurological care. In the operating room, patients underwent standard monitoring including 5-lead ECG, non-invasive blood pressure, oxygen saturation, and end-tidal CO2 via nasal prongs. Choice of the anesthetic regimen was at the discretion of the anesthesiologist in consultation with the neurosurgeon and was either no sedation or conscious sedation with dexmedetomidine. Patients in the DEX group received either a loading dose (0.5 μg/kg over 10 minutes) followed by a maintenance dose ranging from 0.2 μg/kg/hr to 1.0 μg/kg/hr, or just a maintenance dose of the same range as indicated based on the patients' clinical condition. Infusion of DEX was stopped immediately after both burr holes were drilled and the dura was opened, and the remainder of the surgery proceeded without further infusions. No other anesthetic/analgesic agents were used prior to completion of MER, but were administered just after if required. After successful insertion of the DBS electrodes, patients were transferred to the post anesthesia care unit for standard recovery and neurological monitoring.

Surgical Procedure and MERs

MERs were initiated subsequent to the drilling of both burr holes, at which time DEX administration was halted. Stereotactic coordinates of the anterior and posterior commissures (AC and PC, respectively) were identified using magnetic resonance imaging in conjunction with the Leksell model G stereotactic frame. The AC–PC coordinates were used to estimate the location of the GPi 20 mm sagittal sections (Pallidum) of the Schaltenbrand and Wahren atlas.[15] Direct visualization of the target and the trajectory of approach were carried out with commercial planning software on T1–T2 fused images (Stealth Workstation, Medtronic). Tentative GPi 3D coordinates (X,Y,Z) were estimated to be: X = 20 mm lateral to the midline, Y = 0 mm anterior to the midpoint of the AC–PC line (midcommissural point, MCP), and Z = 5 mm inferior to the AC–PC line. MERs and electrical stimulations were used to electrophysiolgically map the targets and their surrounding brain regions as described previously.[16] Two independently driven microelectrodes (25 μm tip lengths, 600 μm apart, 0.2–0.4 MΩ impedances, at 1 kHz), which share a common ground on a stainless-steel intracranial guide tube, were used for recordings and microstimulation. The recordings were amplified 5000 times using two Guideline System GS3000 amplifiers (Axon Instruments, Union City, CA) and initially filtered at 10–3000 Hz and digitized using a CED 1401 data acquisition system (Spike2 v8, Cambridge Electronic Design, Cambridge, UK), then continuously monitored on large LED screen. The GPi was distinguished by having tonically active high frequency discharge neurons (HFD) at 60–80 Hz, with very few pauses in activity seen more characteristically in GPe. Stimulation of GPi cells (150 μs pulse width in a 0.5 second train at 200 Hz using 3–10 μA current) results in a characteristic brief inhibition of activity, which was used for further confirmation of the HFD cell type in GPi. Microstimulation was done

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Table 1: details of anesthetic use for patients in the DEX group

PTN#	Indication for DBS	Age	Sex	Disease Duration (years)	Cells recorded (#)	Loading dose (mcg/kg)	Maintenance dose (high dose vs low dose*)
DEX							
1	PD	65	M	12	19	0.5, 10 minutes	High dose
2	Primary CD	53	F	4	15	0.5, 10 minutes	Low dose
3	Primary CD	50	F	11	14	0.5, 10 minutes	High dose
4	PD	65	F	6	21	none	High dose
5	Primary CD	40	F	10	19	none	Low dose
6	PD	50	M	15	13	none	High dose
7	PD	56	M	7	25	0.5, 10 minutes	Low dose
8	PD	65	F	15	19	none	Low dose
9	Secondary Generalized Dystonia	34	F	7	16	none	High dose
10	PD	65	M	14	3	none	Low dose
No DEX							
1	Primary CD	47	M	12	7	n/a	n/a
2	Primary CD	49	F	19	7	n/a	n/a
3	PD	68	M	23	10	n/a	n/a
4	Primary CD	50	M	7	17	n/a	n/a
5	PD	70	M	16	20	n/a	n/a
6	PD	40	F	9	10	n/a	n/a
7	Secondary Generalized Dystonia	56	F	10	28	n/a	n/a
8	Secondary Generalized Dystonia	65	F	20	13	n/a	n/a

PD = Parkinson's disease; CD = Cervical dystonia.
*high dose: ≥0.6 mcg/kg/hr

using an isolated constant-current stimulator (Neuro-Amp1A, Axon Instruments,) with symmetric, 0.3 ms biphasic pulses (cathodal followed by anodal).

Data Analysis

Using the offline Spike 2 software a band pass filter (300–3000 Hz) was applied to the recordings to reduce background noise. Action potential waveforms from individual neurons were distinguished using the template matching algorithm. Template matching of all recordings was carried out by two independent reviewers in a blinded fashion to reduce bias. Templates were imported into Matlab (v 7.0 Natick MA) and analyzed using an in-house burst detection script that was based on the algorithm developed by Kaneoke and Vitek.[17] The algorithm calculates discharge densities within a specific time interval to detect bursting periods. This time interval is calculated by taking the reciprocal of the discharge rate for a given spike train. The discharge densities are then plotted as a histogram, with high and low densities plotted on the right and left of the histogram, respectively. The shape of the histogram is then compared to a Poisson distribution, and is deemed to contain bursts if its shape differs from that of a Poisson distribution and is positively skewed. Conversely, if the shape of the histogram differs from that of a Poisson distribution and is negatively skewed, it is deemed to fire in a regular pattern. Using this script, we calculated the firing rate, burst index, and firing pattern of GPi neurons. Neurons were classified into one of three categories of firing pattern (regular, bursty, or irregular) based on the discharge density parameters described above.

Statistical Analysis

Statistical analysis was performed using the SPSS (IBM, SPSS statistics, version 24) and Prism (GraphPad, Prism version 7.0b) software. Parametric and non-parametric statistics were used for the analysis of normally and non-normally distributed data, respectively. Continuous variables were assessed using the Mann-Whitney U test or a two-way ANOVA with Tukey's method for testing multiple comparisons. All p-values obtained were therefore adjusted for multiple comparisons. For the analysis of categorical variables, a Chi-square test was used, with the Freeman–Halton extension. Incomplete or missing data were excluded from all analyses.

Results

Demographics

A total of 18 patients underwent bilateral DBS of the GPi, comprising 10 individuals in the "DEX" group (162 GPi cells) and 8 patients in the "No DEX" (112 GPi cells) group (Table 1). The average age of patients in the DEX group was 54.3 ± 11.1 (Mean ± SD) compared to 55.6 ± 11.0 the No DEX group. Of the patients in the DEX group, four (40%) were male, compared to 4 (50%) in the No DEX group. The indication for DBS in each

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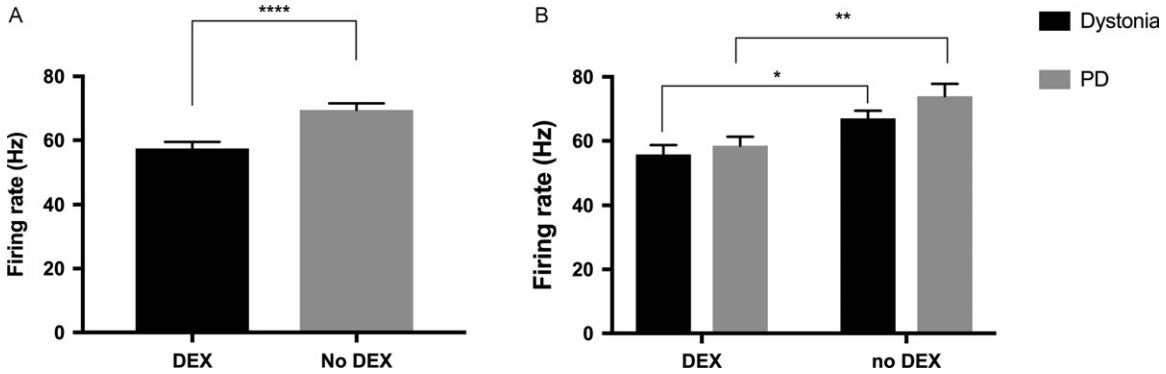

Figure 1: *Firing rates of GPi neurons. (A) difference between DEX and no DEX for all disease groups, P < 00001. (B) Subgroup analysis between PD and dystonia, ** = P < 0.01, * = P < 0.05. All graphs depict means, with error bars showing SEM.*

group was either dystonia or PD. For the patients who were in the DEX group, six had PD (98 GPi cells) and four had dystonia (64 GPi cells); and of the patients who were in the no DEX group, three had PD (40 GPi cells) and five had dystonia (72 GPi cells). Overall, 4 out of 10 patients in the DEX group received loading doses in addition to maintenance doses, while 6 received only maintenance doses.

Mean disease duration was 10.1 ± 4.0 years (mean ± SD) in the DEX group and 14.5 ± 5.8 years in the No DEX group (P = 0.093). For our PD patients, mean disease duration was 11.5 ± 4.0 years in the DEX group and 16 ± 7.0 years in the No DEX group (P = 0.386). Among our dystonia patients, mean disease duration was 8.0 ± 3.2 years in the DEX group and 13.6 ± 5.7 years in the No DEX group (P = 0.107).

The Effect of DEX on GPi Neurons

The mean firing rate of GPi neurons in the DEX group (57.44 ± 2.04; mean ± SEM, n = 162) was found to be lower than the No DEX group (69.53 ± 2.06, n = 112, P < 0.0001, Figure 1A). Although there was a greater time period between the termination of the DEX infusion and MERs obtained from the second GPi of each patient's brain compared to their first, firing rates appeared similar between both sides of the brain. The mean firing rate of neurons from the first GPi of each patient's brain in the DEX group was 57.06 ± 2.732, n = 85, (mean ± SEM) and the mean firing rate from the second side of each patient's brain was 58.07 ± 3.06, n = 77 (P = 0.962). The mean firing rates from both GPi's of each patient's brain were significantly different than firing rates in the No DEX group (Figure S1).

To determine the effects of DEX on the bursting properties of GPi cells, we computed their burst index values (Figure 2) and determined their firing pattern (Figure 3). The mean burst index value of GPi cells in the DEX group was 1.52 ± 0.034, n = 162 (mean ± SEM) vs 1.42 ± 0.025, n = 112 in the No DEX group (P = 0.139). However, a greater proportion of GPi cells were classified as firing in bursty pattern in our DEX group (29.41%) compared to our No DEX group (14.81% P = 0.008). Interestingly, the coefficient of variation (CV) for burst index values was much higher in the DEX group (55.49%), compared to the No DEX group (18.65%). Mean burst index values from the first GPi of patient's brains (1.51 ± 0.05, n = 85) in the DEX group were not significantly different from the mean burst index values of the GPi from the second side of the brain (1.64 ± 0.14, n = 77, P > 0.999, Figure S1). Furthermore, there appeared to be no difference in the firing patterns of GPi neurons between the first and second side of the brain that was recorded from (Figure S2).

Effects in Dystonia and PD Patients

Our analysis showed that the firing rates of GPi neurons in dystonic patients were no different than PD patients in both the DEX group (55.75 ± 2.92 vs 58.53 ± 2.705 dystonia and PD respectively, P = 0.892) and the No DEX group (67.05 ± 2.358 vs 73.98 ± 3.86, dystonia and PD respectively, P = 0.472). However, DEX had a similar effect in both disease states, resulting in a lower firing rate for each group (Figure 1B & Table 2). For dystonic patients DEX resulted in a mean reduction of 11.3 Hz ± 4.150 (P = 0.036), whereas for PD patients, DEX caused a mean reduction of 15.44 Hz ± 4.49 (P = 0.004).

Burst index values were similar in between the DEX and No DEX groups for both dystonia and PD patients (Table 2). However, for both dystonic and PD patients, DEX was associated with a greater proportion of bursty cells and a decrease in the number of regular cells (Table 2 & Figure 3). Upon looking at the spread of data points within each group, we found that the CV was 29.58% for dystonic patients under DEX, compared to 19.75% for dystonic patients under No DEX, and 66.98% for PD patients under DEX compared to 18.89% for patients under No DEX. In light of this, we performed a post-hoc analysis of the difference in the frequency distributions of burst index values for the DEX and No DEX groups using the Kolmogorov–Smirnov test, finding them to be significantly different from each other. (Kolmogorov–Smirnov D = 0.173; P = 0.038). Figure 2 shows box and whisker plots of burst index values for each group.

To compare the relationship between disease severity and firing properties of GPi neurons, we performed a Pearson's correlation between disease duration and firing rates for both PD and dystonia patients (Figure 4). For our PD patients, disease duration was not significantly correlated with a change in firing rates or burst index. This was true in our PD patients who received DEX (r = 0.342, P = 0.507 & r = −0.508, P = 0.304 firing rates and burst indices, respectively) or No DEX (r = −0.557,

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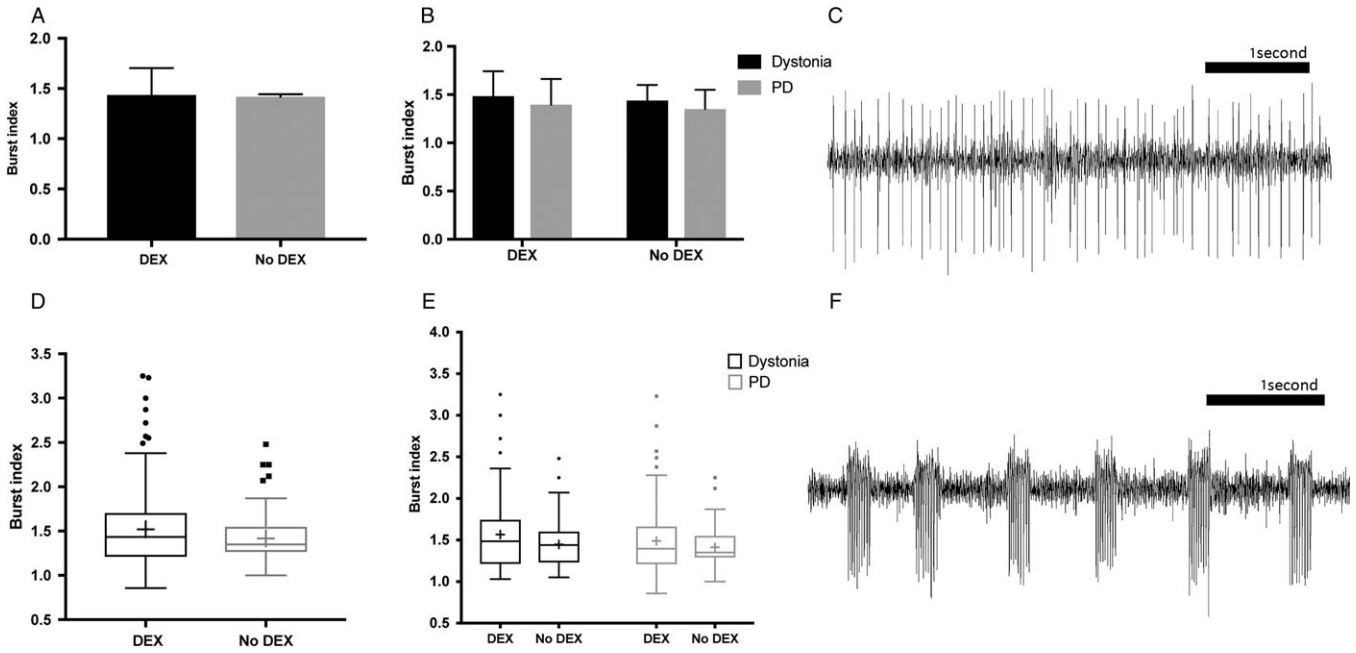

Figure 2: *Burst index values of GPi neurons. (A) The difference in burst index values from GPi neurons in the DEX group and the no DEX group, P = 0.1393. (B) Subgroup analysis of burst index values in PD and dystonia patients, all P values > 0.05. (C) Representative trace recording from a PD patient depicting a cell firing in a regular pattern. (D) Box and whiskers plots (Tukeys method) of burst index values for the DEX and no DEX groups and (E) for disease subgroups. Boxes show the interquartile range, and whiskers extend to Tukey's fences. Horizontal lines depict the median burst index value, (+) signs depict the mean burst index value. (F) representative trace recording from a PD patient depicting a bursty cell.*

P = 0.624 & r = −0.572, P = 0.612, firing rates and burst indices, respectively). This was also true for our dystonia patients; r = 0.246, P = 0.754 and r = 0.087, P = 0.915 for firing fates and burst indices in the DEX group, respectively. For dystonia patients in the No DEX group, r = −0.337, P = 0.580 and r = −0.132, P = 0.833 for both firing rates and burst indices, respectively.

The Relationship between DEX Dose and GPi Firing Properties

We investigated the effect of DEX maintenance dose on the firing rate and burst index of GPi neurons. Maintenance doses were stratified into two categories; high dose (≥0.6 μg/kg/hr) and low dose (<0.6 mcg/kg/hr). Five patients received a high dose of DEX, while five received a low dose of DEX. With regards to firing rates, we found a significant decrease in the High DEX group compared to the Low DEX group (Figure 5), with mean firing rate in the High DEX group being 51.56 ± 3.37 (mean ± SEM) compared to 61.22 ± 2.44 in the Low DEX group (P < 0.01). This was true for our dystonia patients as well, but not for our PD patients. The mean firing rate for dystonia patients in the high DEX group was 49.10 ± 4.97 vs 63.42 ± 5.06 in the low DEX group (P < 0.01).

The low dose DEX group for dystonic patients was also associated with a higher mean burst index value (1.72 ± 0.090; mean ± SEM) when compared high DEX groups (1.39 ± 0.056; P = 0.0006, Figure 5D).

Furthermore, we performed a correlation of firing rates and burst indices with DEX maintenance dose. While the analysis revealed a trend for lower firing rates (r = −0.346) and burst indices (r = −0.152) at higher DEX doses, it did not reach statistical significance (P = 0.330 & P = 0.682 for firing rates and burst indices, respectively).

Discussion

The use of DEX for DBS has been increasing in popularity, primarily due to its non-opioid, non-GABAergic mediated sedation which distinguishes it from other sedative/hypnotics such as propofol and benzodiazepines.[11,18] Previous studies on the effects of DEX in basal ganglia structures have produced mixed results, and a dose response effect has been proposed.[18,19] Here we show that it may be associated with modulating the firing rate and bursting properties of GPi cells in both dystonic and PD patients.

In both PD and dystonia patients, DEX was associated with lower firing rates. While DEX did not impede the procurement of MERs, it does have implications for the interpretation of the data in the context of disease. For instance, under DEX, both PD and dystonia firing rates were found to be not significantly different from each other (P > 0.889, Figure 1B). This is in contrast to previous studies that have shown a reduction in the mean discharge rate of GPi neurons in adults with dystonia compared to non-human primates, or individuals with PD. Therefore it is helpful to take into account anesthetic use when investigating the neurophysiology of these disorders.[20,21] Stratification of our DEX patients into low dose and high dose groups revealed a trend that favored decreased firing rates at high doses of DEX (Figure 5). Furthermore, a recent study has shown a correlation between GPi firing rates and DBS outcome in dystonic children.[22] This suggests that real time analysis of GPi firing rates can be used to predict responses to DBS, and therefore may

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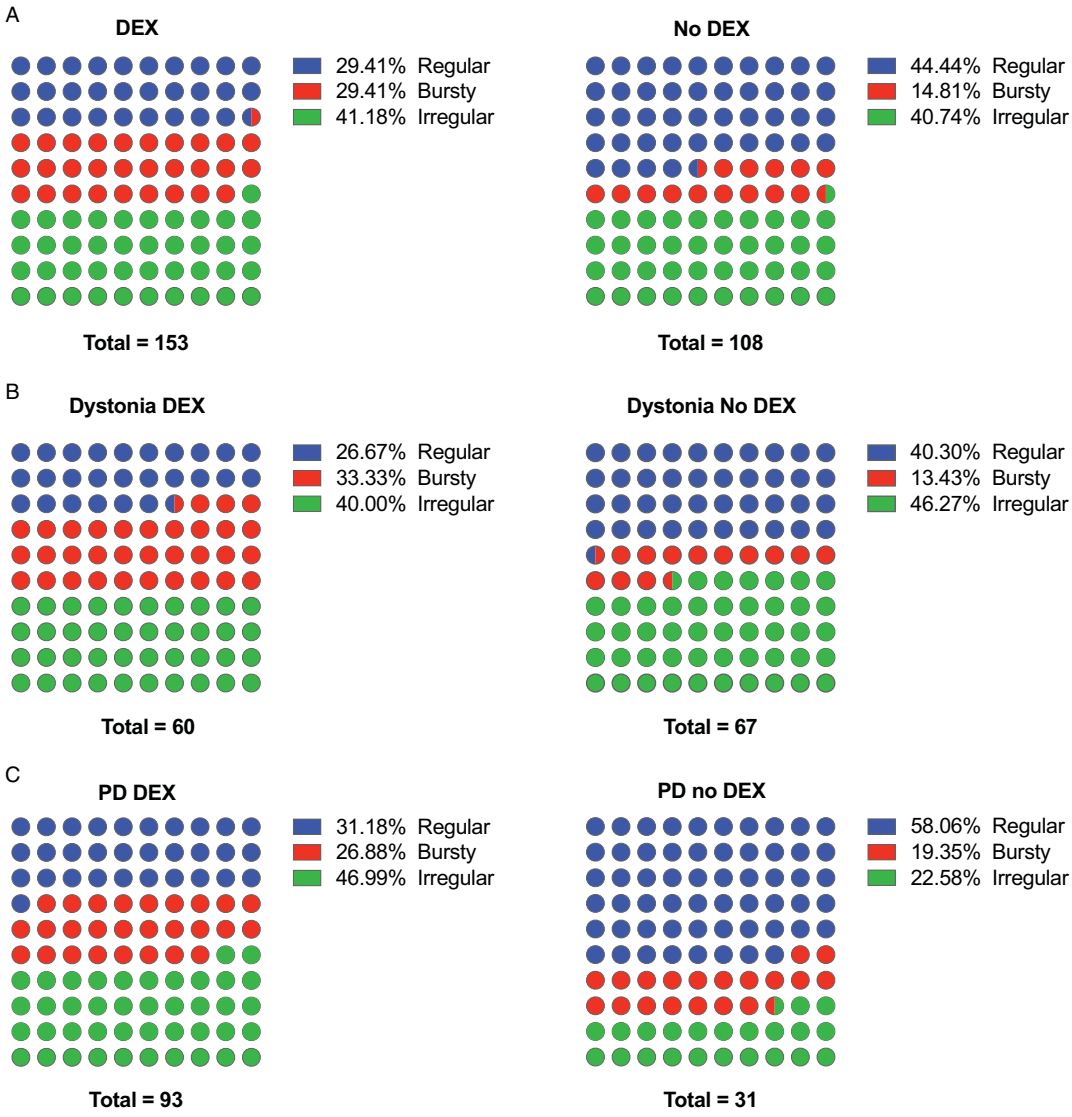

Figure 3. *10 × 10 dot plots depicting the relative proportion of GPi Firing patterns. Each dot corresponds to 1% of the neurons obtained from each group, the total corresponds to the total number of neurons sampled. (A) DEX vs No DEX, P = 0.008. (B) The effect of DEX on GPi firing patterns in dystonic patients, P = 0.023. C) The effect of DEX on GPi firing patterns in PD patients, P = 0.043.*

even serve as a guide for more individualized neuromodulation in the future. Understanding the effects of anesthetics on MERs could help improve the accuracy of such predictions.

DEX was also associated with a greater percentage of cells firing in a bursty manner, and a lower percentage of cells firing in a regular manner. Interestingly, we did not observe a significant difference in the mean burst index values between our DEX and No DEX groups; however, we did observe an increase in the variance among burst index values seen in the DEX group. It may be that certain cells within the GPi display an increased sensitivity to dexmedetomidine, potentially due to variations in afferent connections. Furthermore, the effects of DEX on GPi neurons from PD and dystonic patients were similar, considering that these disorders are symptomatically dissimilar. However, there appeared to be a dose-related effect of DEX on the burst index of GPi cells in our dystonia group only. GPi cells from dystonic patients were associated with higher burst indices at a low dose of DEX, compared to a high dose of DEX (Figure 5D). Future studies should examine whether the neuronal response to DEX varies in relation to the region of the GPi from which the MER's are obtained.

In addition to functioning as auto-receptors, alpha-2 adrenergic receptors can be located postsynaptically, where they function to reduce neuronal excitability by hyperpolarizing the membrane.[23,24] Future studies should examine whether or not this is responsible for the effects of DEX seen here. It may be that DEX's effects on the robustness of MERs are mediated in part by its effects on behavioral arousal.[25] This could also explain why we observed an increase in burst index at lower doses of DEX.

Krishna et al reported increased firing rates and a decrease in the burstiness of STN cells from PD patients who were under DEX, compared to those who were not.[7] A recent study investigating the effects of DEX on MERs in parkinsonian patients also found GPi firing rates to be reduced, with more pauses in spike

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Table 2: Firing rates, burst index and firing pattern of GPi neurons for PD and dystonia patients. Values for firing rates and burst indices are presented as mean ± SE. P values correspond to differences in the mean values for the DEX and No DEX groups in each row

Measure	Dystonia					PD				
	No DEX	n	DEX	n	P	No DEX	n	DEX	n	P
Firing rate	67.05 ± 2.358	72	55.75 ± 2.92	64	0.036	73.98 ± 3.86	40	58.53 ± 2.705	98	0.004
Burst index	1.42 ± 0.037	72	1.57 ± 0.058	64	0.572	1.41 ± 0.042	40	1.49 ± 0.041	98	0.554
Firing pattern	Bursty: 13.4%	67	Bursty: 33.3%	60	0.023	Bursty:19.4%	31	Bursty:26.9%	93	0.043
	Irregular: 46.3%		Irregular: 40%			Irregular: 22.6%		Irregular: 47.0%		
	Regular:4 0.3%		Regular: 26.7%			Regular:58.0%		Regular:31.1%		

PD = Parkinson's disease.

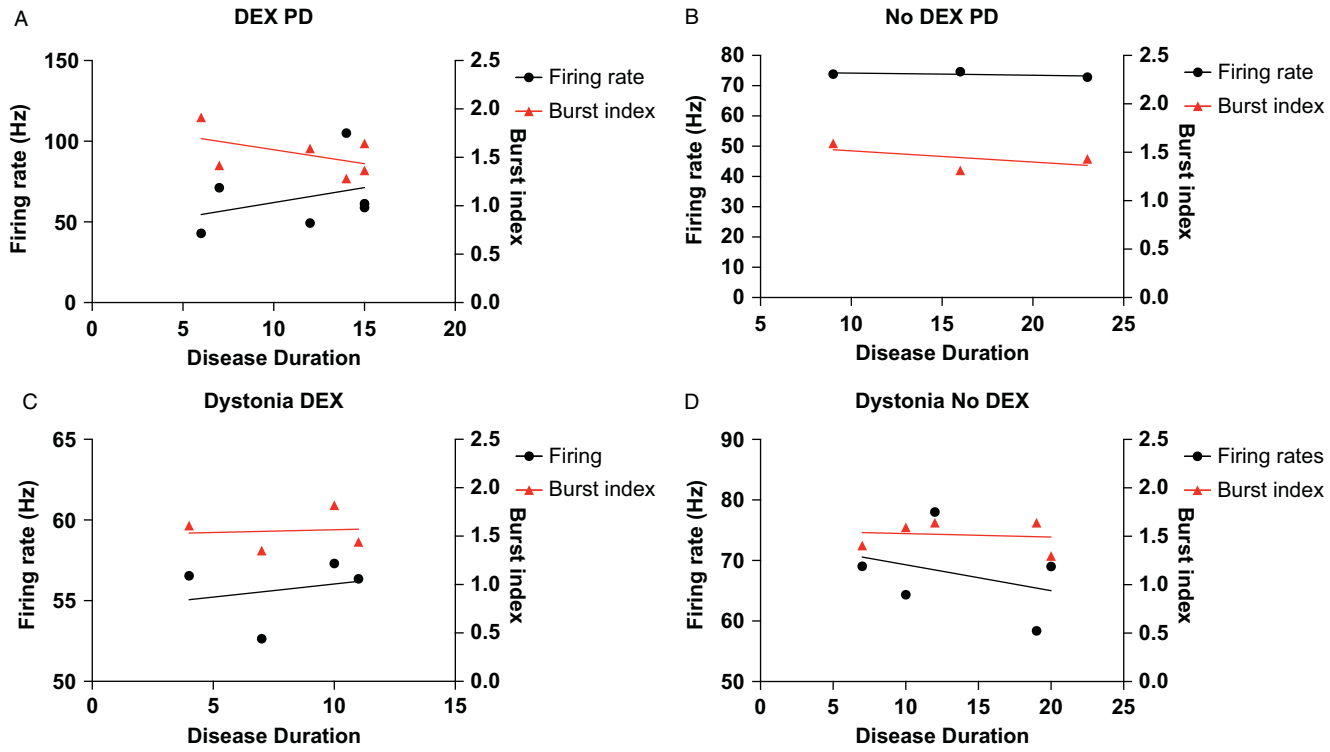

Figure 4: Lack of correlation between disease duration and firing properties in GPi neurons in PD and Dystonia patients. Scatter plots of firing rate and burst indices for patients in the PD (A&B) and Dystonia (C&D) groups, and corresponding lines of best fit. All graphs depict relationships with non-significant Pearson correlation coefficients (P > 0.05 for all graphs).

trains under DEX compared to local anesthetic.[8] Unlike the STN, the GPi does not receive substantial noradrenergic innervation from the Locus Coeruleus.[12,13] The effects of DEX on GPi neurons could be mediated indirectly through the inhibition of brain regions innervated by the Locus Coeruleus, such as the striatum, STN, or cortex. A recent study has also shown that the tonic inhibitory activity of the subthalmo-cortical loops is coupled to the noradrenergic system, and that this activity can be modulated using the alpha-2 adrenergic agonist clonidine.[26] Furthermore, the alpha-2 antagonist idazoxan has been shown to reduce extracellular levels of striatal dopamine, and consequently reduce the effects of L-Dopa-induced dyskinesias, thus showing that modulation of alpha-2 receptors in the basal ganglia has the potential to modulate dopamine signaling and therefore neuronal activity in the basal ganglia.[27] Accordingly, dopaminergic manipulations through the inhibition of tyrosine hydroxylase and the use of D1/D2 receptor antagonists have been shown to alter neuronal firing patterns in the basal ganglia, including the GPi.[28]

Alternatively, the effect of DEX on neuronal activity in the GPi could be explained by a direct activation of locally expressed alpha-2 receptors. Between the three subtypes of alpha-adrenergic receptors, the alpha-2c subtype has been found to be highly expressed in the basal ganglia.[29]

The main limitations of our study arise due to its retrospective nature. DEX doses were not under our control and three of our patients who had received DEX also received fentanyl or propofol, although this was administered after MERs were procured.

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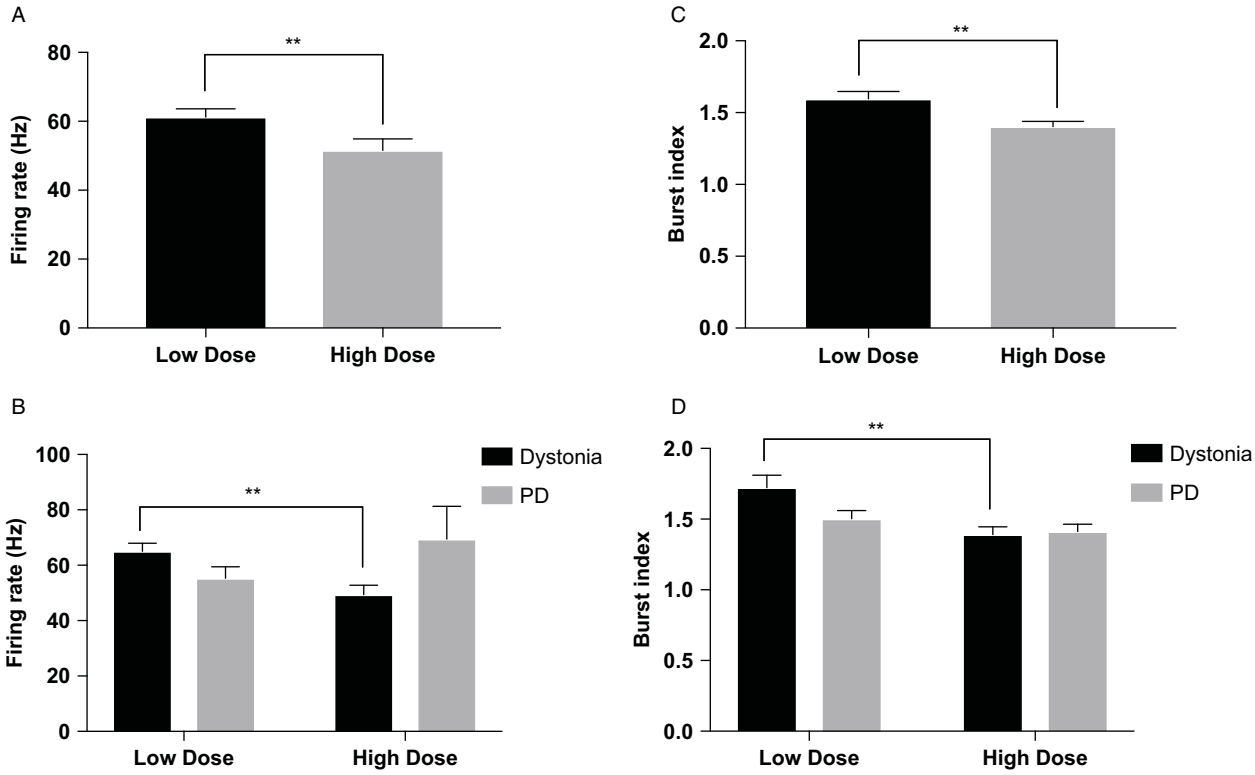

Figure 5: *The effect of DEX dose on GPi firing properties. (A) Firing rates; DEX vs No DEX. (B) The effect of DEX dose on the firing rates of GPi neurons in Dystonia and PD patients. (C) Burst index; DEX vs No DEX. (D) The effect of DEX dose on the burst index of GPi neurons in dystonia and PD patients. ** $P < 0.01$ for all graphs.*

Furthermore, we were not able to obtain data regarding the state of arousal for patients during the procedure, or on the temporal relationship between DEX infusion and MERs. Due to DEX's half-life, its effects on MERs might vary depending on the amount of time that has passed between the termination of the infusion and the procurement of MERs. The length of time between terminations of the DEX infusion varies slightly depending on the amount time it takes to clean the burr hole, place the frame on the patients head, and attach the recording equipment, and is usually between 10 and 15 minutes. Since both burr holes are drilled first and MERs procured subsequently, there also exists a greater time gap between the procurement of MERs from the first GPi of each patient, compared to their second. We therefore investigated the difference in the firing properties of GPi neurons recorded from the first side of the patient's brain with the second side of the patient's brain, and found no significant difference. It is possible that the duration of time taken to complete the recording component of the procedure is not sufficiently long enough to correspond with a meaningful reduction in the effects of DEX, and this should be verified in future studies. The decision for using DEX during the procedure is made at the discretion of the anesthesiologist, and is ultimately done for its clinical utility. Factors influencing this decision include patient comfort, hemodynamic stability and the presence of tremor or dystonia. These could have created a source of bias in our results and future studies should examine the effects of DEX prospectively, allowing for more control over these variables.

To determine whether the use of DEX was related to disease severity, we compared the mean disease duration between our DEX and no DEX groups and found no significant difference. Furthermore, we investigated the relationship between disease severity and firing properties of GPi neurons. We did not find any statistically significant correlation between firing properties and disease duration for both dystonia and PD patients, which could have likely been due to the small sample size of our group; however, a lack of correlation between motor symptoms and electrophysiological recordings within the GPi of dystonia patients has previously been demonstrated.[30] Conversely, previous studies in PD patients have demonstrated a correlation between motor symptom severity and firing properties.[31,32] While our PD patients displayed a trend favoring higher firing rates and lower burst indices at longer disease durations, it was not statistically significant, possibly due to the small sample size.

The effects of DEX on GPi neurons from PD and dystonia patients were similar, considering that these disorders have fundamentally different and somewhat opposing neurophysiological mechanisms. We report that DEX is associated with a decrease in GPi firing rates and may be associated with an increase in burstiness.

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the data collection and the functional neurosurgical fellows for performing the surgical procedures.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Statement of Authorship

MG: This author was involved in performing data analyses and drafting the manuscript. SK, MH AND AL: This author was involved in the surgical procedures and data collection. LV: This author was involved in the surgical procedures and data collection as well as manuscript drafting. WH: This author was involved in the surgical procedures and data analysis as well as manuscript drafting and revisions

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2020.243.

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