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Pallidal stimulation: Effect of pattern and rate on bradykinesia in the non-human primate model of Parkinson's disease

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Abstract

Deep brain stimulation (DBS) involves the delivery of continuous, fixed-frequency electrical pulses to specific brain regions; however the reliance of therapeutic benefit on the fixed-frequency nature of the stimulation pattern is currently unknown. To address this, we investigated the effect of changes in the pattern and frequency of DBS in the internal segment of the globus pallidus (GPi) on bradykinesia in a single, hemi-parkinsonian monkey. Therapeutic parameters (i.e., contacts, pulse width, amplitude) were established for fixed-frequency stimulation at 135 Hz based on improved movement times during a reach and retrieval task. Thereafter, the pattern and frequency of stimulation was varied to assess the effect of variability, bursting and oscillatory patterns of stimulation on bradykinesia. During fixed-frequency stimulation, performance improved as a function of increasing pulse rate ($p < 0.01$). Using a temporally irregular pattern at the same average frequency failed to alter therapeutic benefit relative to the fixed-frequency condition. Introducing an 80 Hz burst pattern (20 bursts/second at 4 pulses/burst) improved bradykinesia ($p < 0.01$) relative to both “OFF” and 80 Hz fixed-frequency conditions, yielding results comparable to fixed-frequency stimulation at 135 Hz with 40% less current drain. Compared to burst and fixed-frequency stimulation, oscillatory patterns at 4 and 8 Hz were less effective. These results suggest that lower frequency stimulation delivered in a regular bursting pattern may be equally effective and require lower energy than higher frequency continuous patterns of stimulation, thereby prolonging battery life and call into question the role of bursting activity in the pathogenesis of bradykinesia.

Keywords

deep brain stimulation; globus pallidus, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); monkey; Parkinsonism

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) is an effective treatment for patients with Parkinson's disease (PD), yielding improvements across the spectrum of cardinal motor features, including tremor, rigidity, bradykinesia and akinesia (Moro, et al., Rodriguez-Oroz, et al., 2005). Benefit typically is achieved through the delivery of temporally-regular, pulsed stimulation at rates

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of 90 Hz or higher (Rodriguez-Oroz, et al., 2005). Early work by Benabid and colleagues (Benabid, et al., 1991) characterized the effect of pulse frequency during DBS of the ventral intermediate nucleus (VIM) of the thalamus for tremor as a U-shaped curve; with control appearing at approximately 60 Hz, peaking at 150 Hz and diminishing again at extremely high pulse frequencies (~1,000 Hz). That work has since been extended to the effect of STN DBS on parkinsonian motor signs, where a similar frequency-response curve has been reported (Fogelson, et al., 2005, Moro, et al., 2002); however data on the higher frequency range (i.e., > 185 Hz) is lacking due primarily to the upper frequency limit of current implantable pulse generators (IPG). Interestingly rather than simply being ineffective, stimulation frequencies at the lower end of the range (<60 Hz) have been shown to worsen tremor, akinesia (Moro, et al., 2002, Timmermann, et al., 2004) and bradykinesia (Fogelson, et al., 2005, Timmermann, et al., 2004). While the mechanism of this effect is not known, it has been proposed to occur as a result of either the direct activation of corticomotor circuits or through interaction with, or reinforcement of, existing pathological rhythms (Fogelson, et al., 2005, Kuhn, et al., 2008, Timmermann, et al., 2004).

Hypotheses relating to the pathophysiology of PD have shifted over the past decade from a focus on changes in mean discharge rate within specific regions of the pallidothalamocortical network (Miller and DeLong, 1988) to changes in the pattern of neuronal activity and the development of synchronized oscillations across the network (Brown, 2003). Similarly, mechanistic hypotheses pertaining to DBS have shifted from inhibition of somatic activity within the targeted subcortical nucleus to theories based upon data that shows that DBS activates target output (Hashimoto, et al., 2003, Johnson, et al., 2009) and imposes the more regular, high-frequency DBS signal on downstream nodal points. The overall role of such activation in therapeutic efficacy remains unclear, though several theories suggest that stimulation overrides abnormal neuronal activity present in the network. This is supported by reports from Birdno and colleagues (Birdno, et al., 2007, Birdno, et al., 2008), whose data suggest that the efficacy of VIM DBS for tremor depends upon the regularity of the pulse train, with variations in the inter-pulse interval, either systematic or randomized, reducing therapeutic benefit. Similarly, Dorval et al (Dorval, et al., 2010) observed a worsening of bradykinesia with increasing temporal irregularity of stimulus pulses during STN DBS in patients with PD. The goal of this study was to investigate the role of changes in the pattern and rate of GPi DBS on bradykinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) non-human primate model of PD. A better understanding of how changes in the pattern of stimulation influences both therapeutic benefit and the appearance of side effects may help to improve efficacy as well as to provide insight into the mechanism of action of DBS.

Materials and Methods

All surgical and behavioral protocols were approved by the Institutional Animal Care and Use Committee and complied with United States Public Health Service policy on the humane care and use of laboratory animals. A single adult rhesus monkey (*Macaca mulatta*; female, 6.0 kg) was used. All surgical procedures were performed using sterile technique under aseptic conditions with isoflurane anesthesia (2%-5%).

Surgical Procedures

Details related to the induction of the hemi-parkinsonian state (Xu, et al., 2008) and the placement of the cephalic chamber have been reported previously (Elder, et al., 2005, Miocinovic, et al., 2007). Briefly, the monkey was treated with MPTP (0.1% solution in saline) via unilateral, intracarotid injection (0.4 – 0.65 mg/kg over 15 minutes). The procedure was repeated until a stable hemi-parkinsonian state was achieved, as characterized by the presence and persistence of contralateral rigidity and bradykinesia.

During a separate surgical procedure, and with the head secured in a primate stereotaxic frame, a craniotomy was performed over which a cephalic recording chamber directed at the GPi was placed along the coronal plane at an angle of 30° off of midline. Titanium screws were secured at specific points across the calvaria to serve as anchor points and were bonded together with the recording chamber and a head stabilization receptacle using dental acrylic. During a 2-week postoperative recovery period, the monkey was given prophylactic analgesics and antibiotics as well as ad libitum access to food and water.

Pallidal mapping and DBS lead placement

After recovery, the pallidal region was mapped in the awake, restrained animal using extracellular microelectrode recording techniques similar to those applied during human functional neurosurgery (Vitek, et al., 1998). Glass-insulated platinum-iridium microelectrodes (impedance 0.5–1.0 MΩ at 1 kHz) were advanced using a hydraulic micro-drive (Model MO-95, Narishige International, Inc.) attached to the chamber. The animal was conditioned through positive reinforcement to allow manipulation of its upper and lower extremities to facilitate identification of the sensorimotor region. Once the posterolateral, sensorimotor region of the GPi was identified, a scaled down version of the human DBS lead was implanted such that the distal tip was situated 1.0 mm above the level of the optic tract (Elder, et al., 2005). The lead consisted of four, cylindrical platinum-iridium contacts numbered 3 through 0 in the dorsal to ventral direction, with each contact 0.62 mm in diameter, 0.5 mm tall and separated by 0.5 mm. Once in position, the proximal end was secured to a custom-made ring placed within the recording chamber using dental acrylic. Two weeks after implantation, therapeutic parameters were determined for stimulation at 135 Hz through serial evaluation of changes in bradykinesia and rigidity by an investigator blinded to the stimulation settings (Hashimoto, et al., 2003). Therapeutic parameters were defined as those settings that provided the greatest motor benefit without observable side effects at a fixed-frequency pulse rate of 135 Hz. Once identified, the associated pulse width, lead contacts and stimulus amplitude were held constant throughout the remainder of experimental testing, with changes limited to the frequency and pattern of pulse delivery.

Behavioral Assessment

Bradykinesia was quantified by measuring the time required to retrieve food rewards from a modified Klüberboard comprised of three linearly-spaced wells, where each well is 2 cm in diameter, 3 mm deep and separated by 3 cm. The animal was presented with the baited Klüberboard in a standardized manner with one arm restrained and allowed to pick the pieces of food from the wells using the unrestrained arm. Monkeys were timed from initial contact with the first piece of food until contact with the mouth with the last piece, with the time required to make all three movements recorded as the total movement time for that trial. Two conditions were applied per daily testing session, with order of presentation randomized between sessions.

In addition to the effect of changes in frequency of stimulation during isochronal stimulation, we examined three variations in the temporal pattern of the pulses on bradykinesia: irregularity (i.e., random inter-pulse interval), bursting and oscillation. The irregular pattern was created by drawing inter-pulse intervals from a Gaussian distribution centered on 7.4 ms with a coefficient of variation of 0.47. This value was selected as the maximal degree of irregularity that could be achieved without pulse overlap in the stimulus train. A 20 Hz burst stimulation condition was constructed using an average overall pulse rate of 80 Hz, with pulses clustered into twenty bursts of four pulses per burst with an intra-burst rate of 167 Hz. The temporal pattern of the bursts was either regular or irregular, with regular bursts delivered at a rate of 20 bursts per second while the inter-burst interval for the irregular condition was again drawn from a Gaussian distribution. Finally, the oscillatory

pattern was created through successive narrowing and expansion of the inter-pulse interval around a peak oscillatory frequency of 4, 8 or 17 Hz.

Data Analysis

For each condition, behavioral outliers in the movement time data were identified using the inter-quartile range method ($> 1.5 \times \text{IQR}$) (Wilcox, 2005) and excluded from further analysis. Statistical comparisons of total movement time between stimulation conditions were made using Kruskal-Wallis analysis of variance on ranks, with multiple comparisons corrected using Dunn's Method ($p < 0.05$).

Results

Maximal therapeutic effect using a fixed-frequency pulse rate of 135 Hz was observed at 2.0 mA using contact 0 as the cathode and 1 as the anode (pulse width: 90 μsec). A total of 2,721 trials were collected across the different stimulation conditions over a period of six months, of which 246 (9%) were discarded as behavioral outliers.

Irregular Stimulation

Temporally regular stimulation in GPi was associated with frequency-dependent improvements in bradykinesia, as signified by a 13%, 23% and 35% reduction in the median movement time relative to DBS OFF (Median = 6.10; IQR = 5.10 to 7.25) for stimulation at 50 (Median = 5.31; IQR = 4.62 to 6.20), 80 (Median = 4.72; IQR = 4.09 to 5.32) and 135 Hz (Median = 3.97; IQR = 3.10 to 5.60), respectively (Figure 1A). There was a significant main effect for pulse frequency ($H_3 = 171.82$, $P < 0.001$) and post-hoc comparisons made using Dunn's method identified a significant difference between all levels of stimulation with the exception of the 80 Hz and 135 Hz condition. However, there was a substantial trend observed between the 80 Hz and 135 Hz condition, marked by a 19% improvement in median movement time at 135 Hz relative to 80 Hz. Making the GPi DBS pulse train temporally irregular at 50 (Median = 5.02, IQR = 4.42 to 5.84), 80 (Median = 4.78, IQR = 4.04 to 5.70) or 135 (Median = 4.44, IQR = 3.62 to 5.40) Hz improved movement times but were not significantly different from (Figure 1B) the fixed-frequency stimulation condition.

Burst Stimulation

The 80 Hz burst condition (20 bursts/sec with 4 stimulation pulses/burst) improved median movement time (Median 3.94; IQR = 3.37 to 4.67) relative to both the DBS OFF ($P < 0.001$) and the 80 Hz regular ($P < 0.001$) conditions (Figure 1C), and did not differ significantly from improvement observed with stimulation at a regular pulse rate of 135 Hz ($P = 0.61$). Delivering the same four-pulse bursts in a temporally irregular (i.e., variable inter-burst interval) pattern revealed a similar effect, as the 80 Hz irregular bursting pattern (Median = 4.05; IQR = 3.28 to 4.78) improved movement times relative to DBS OFF ($P < 0.001$) and 80 Hz regular ($P < 0.001$) stimulation and again produced an effect that did not differ significantly from DBS at a regular pulse rate of 135 Hz ($P = 0.60$).

Oscillatory Stimulation

The ANOVA model revealed a significant main effect for the frequency of the oscillatory pattern used during the modulated stimulation condition relative to fixed-frequency stimulation at 135 Hz ($H_3 = 16.64$, $P < 0.001$). As illustrated in Figure 1D (top), an inverse relationship was observed such that decreasing the oscillatory frequency from 17 Hz (Median = 4.5; IQR = 3.97 to 5.28) to 8 Hz (Median = 4.72; IQR = 3.98 to 5.52) to 4 Hz (Median = 4.85; IQR = 4.35 to 5.43) was associated with a corresponding increase (i.e., worsening) in median movement time, though even the 4 Hz condition tended to improve

motor performance relative to the DBS OFF condition. Relative to the 135 Hz stimulation condition, post-hoc comparisons revealed that the absolute difference in median movement time was significantly worse for oscillatory stimulation at 4 Hz ($P < 0.05$) and 8 Hz ($P < 0.05$) but not 17 Hz. As illustrated in **Figure 2b** (bottom), a similar, significant effect ($H_3 = 12.16$, $P = 0.002$) was observed for oscillatory stimulation with an average pulse rate of 80 Hz, though in this case post-hoc comparisons found that an oscillatory frequency of 4 Hz (Median = 5.22; IQR = 4.68 to 6.12) produced a significant worsening of median movement time while 8 Hz modulation did not (Median = 4.88; IQR = 4.12 to 5.58).

Discussion

In the current report, we present data on the effect of variations in the rate and temporal pattern of GPi DBS on bradykinesia in the MPTP monkey model of parkinsonism. Relative to the therapeutic effect observed when using a temporally-regular stimulation condition, changes in the temporal pattern of GPi DBS using the same average frequency could either improve, worsen or produce a comparable level of improvement in performance on the reach and retrieval task. Consistent with human trials of GPi DBS (Moro, et al., 2010), a 35% reduction in total movement time was observed during fixed-frequency, 135 Hz stimulation in the single animal studied. Similar to observations made during STN and VIM DBS in humans (Benabid, et al., 1991, Fogelson, et al., 2005, Moro, et al., 2002) the efficacy of fixed-frequency stimulation was sensitive to pulse rate, marked by step-wise improvements in motor performance as a function of increasing frequency. The consistency of these fixed-frequency findings across the two species lends further support to the validity of the non-human primate MPTP model for investigation of DBS mechanisms in general and the effect of changing patterns of stimulation in particular.

Temporally irregular stimulation patterns did not influence therapeutic efficacy relative to the corresponding fixed-frequency condition for any of the three frequencies examined. This finding contrasts with prior results during STN DBS in patients with PD, where irregular stimulation was found to reduce therapeutic efficacy for tremor (Birdno, et al., 2007, Birdno, et al., 2008) and bradykinesia (Dorval, et al., 2010). During intra-operative testing of PD patients who were undergoing surgery to replace their implantable pulse generator (IPG), Dorval et al. (Dorval, et al., 2010) observed a positive relationship between variance in the inter-pulse interval of STN stimulation and worsening of bradykinesia. Although the reason for the difference in findings is not clear, it may be related to differences in the model evaluated, the method of evaluation, or the target of stimulation (i.e., STN vs. GPi). A possible target-related explanation may be due to the difference in the time course of the postsynaptic potentials (PSP) produced during DBS, given previous reports that DBS activates output from the stimulated structure (Anderson, et al., 2003, Hashimoto, et al., 2003, Xu, et al., 2008). Birdno et al. propose that prolonged pauses in the pulse train during STN DBS may either be ineffective at masking the pathological activity patterns present in the pallidothalamocortical network or, conversely, may permit a type of release phenomenon within the pallidal receiving area of the thalamus, producing a rebound, bursting phenomena that reduces thalamic fidelity (Birdno, et al., 2007). In the case of GPi however, the inhibitory PSP produced by activation of the GABAergic pallidal output would be expected to outlast the glutamatergic PSP from STN stimulation by up to an order of magnitude (Castro-Alamancos and Connors, 1997), an effect that may minimize the impact of irregularity in the GPi DBS stimulus train.

Current hypotheses regarding the pathophysiology of PD implicate increased bursting and synchronized oscillatory activity within defined power spectrums in the pallidothalamocortical network (Brown, 2003, Devos, et al., 2004). We sought to test this hypothesis by clustering stimulus pulses during GPi DBS into brief, high-frequency bursts

or into oscillatory patterns and examining their effect on movement time relative to the fixed-pulse rate condition of the same average frequency. Contrary to our prediction that such changes would worsen motor performance, we observed improvements in movement times that were, in some cases, comparable to that observed during fixed frequency stimulation. Indeed, a bursting pattern of stimulation incorporating 20 bursts/second with 4 pulses/burst for an overall frequency of 80 Hz proved equally as effective as 135Hz in a regular pattern theoretically saving battery life due to lower current requirements. While the mechanism of the observed enhancement is not clear, it too may result from the differences in the temporal dynamics of the first order synapse, an effect that is perhaps compounded by a cumulative effect (i.e., temporal summation) produced by the relatively high intra-burst frequency (Kaneoke and Vitek, 1996).

Finally, a reduction in therapeutic efficacy relative to the fixed-frequency condition was observed when the pulse sequence was delivered using the oscillatory pattern, regardless of whether the average pulse rate was 80 Hz or 135 Hz. In all cases, the presence of the slower, underlying modulation rate reduced therapeutic efficacy relative to the corresponding fixed-frequency condition. Performance during the modulated condition was still improved however, relative to the DBS off condition. Indeed, although an exhaustive pattern search was not made, none of the pattern variations examined in this study yielded a worsening of bradykinesia beyond that observed during the baseline, DBS OFF condition. One possible explanation for this lack of worsening may be that parkinsonian motor signs derive from a the combination of changes in the pattern of pallidothalamocortical network activity (e.g., bursting together with synchronized oscillations), while in the current study the effect of only a single pattern was evaluated during each experimental condition. Alternatively, we cannot be sure that the pattern of stimulation applied in the present study yielded similar changes in downstream structures, which would have required recording from structures downstream from the site of stimulation. Nonetheless it was noteworthy that inserting burst and oscillatory patterns of stimulation at frequencies associated with the development of parkinsonian motor signs improved bradykinesia and reminds one that previously conceived notions of the pathophysiological basis for PD motor signs remain ill-defined. These data suggest that development of technology to allow exploration of different patterns of stimulation are important to the optimization of this therapy for PD as well as for other neurological disorders.

Conclusions

The present study supports the hypothesis that the temporal pattern of stimulus pulses applied during GPi DBS can influence the therapeutic efficacy of this treatment approach. The current results are limited both by the single case nature of the data set as well as the assessment of only a single parkinsonian motor sign, bradykinesia. There is a need for replication of these data as well as exploration of additional pattern variations derived from known pathophysiological changes in the pallidothalamocortical network in PD. Moreover, the effect of these pattern variations on neuronal activity at nodal points throughout the circuit needs to be investigated and compared to that reported for fixed-frequency pallidal stimulation (Anderson, et al., 2003, Johnson, et al., 2009). Regardless, the current data suggest that maximal therapeutic effect for GPi DBS is not uniquely dependent upon the application of a fixed-frequency signal, leaving open the possible existence of stimulation patterns that may further optimize clinical benefit, possibly with reduced cost to battery life. Advances in our awareness of the influence of stimulation pattern on therapeutic efficacy may improve our understanding of the relationship between neuronal activity changes in the paladothalamocortical network and the development of bradykinesia and rigidity, and provide greater insight into the mechanisms underlying the effect of DBS. Finally, although the magnitude of the therapeutic effect was greatest for the 135 Hz fixed-frequency

condition, the lack of a significant difference in motor performance between that pulse rate and the 80 Hz fixed-frequency condition could have immediate clinical implications. The potential impact on battery life between these two pulse rates suggests that more emphasis should be placed on identifying the minimal effective pulse rate for each patient, rather than simply setting the IPG to a predetermined pulse rate of 130 Hz or even higher.

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Figure 1.

Effect of varying frequency and pattern on reach and retrieval task performance in the MPTP NHP. **A)** Temporally regular deep brain stimulation of the internal segment of the globus pallidus was associated with frequency specific improvements in bradykinesia in the MPTP monkey. Reach and retrieval times improved as a function of increasing stimulation frequency, however the trend of improved motor performance between the 80 Hz and 135 Hz was not found to be significant. **B)** The temporal regularity of the pulse train delivered during deep brain stimulation of the internal segment of the globus pallidus did not influence the motor improvements observed at any of the three levels of stimulation frequency. The

series of box plots compare motor performance between the temporally regular and irregular pattern for average frequencies of 50 Hz (top), 80 Hz (middle) and 135 Hz (bottom). The bar chart to the right of each box plot shows an example inter-pulse interval histogram during the irregular stimulation condition. **C)** Burst pattern stimulation with an average frequency of 80 Hz improved reach and retrieval performance relative to temporally regular stimulation at 80 Hz regardless of whether the burst pattern was temporally regular or irregular. Regular and irregular burst stimulation improved median motor performance by 35.4% and 33.6%, respectively, relative to the DBS OFF condition and by 16.5% and 14.2%, respectively, relative to the temporally regular stimulation at 80 Hz. In both instances, burst pattern stimulation produced motor effects comparable to that observed during temporally regular stimulation at 135 Hz. *Significant differences from the DBS OFF condition. #Significant differences from temporally regular DBS at 80 Hz. **D)** Arrangement of the pulse sequence into an oscillating pattern reduced the efficacy of GPi DBS relative to temporally regular stimulation at the same average frequency. For both the 135 Hz (top) and 80 Hz (bottom) condition, the effect on motor performance was dependent upon modulation frequency such that lower frequencies were associated with an increase in mean reach and retrieval time. *Significant differences from the temporally regular DBS condition. For all figures, the y-axis represents movement time in seconds. * $p < 0.05$