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DEEP BRAIN STIMULATION IMPROVES MOVEMENT AMPLITUDE BUT NOT HASTENING OF REPETITIVE FINGER MOVEMENTS

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Abstract

External pacing cues, dopaminergic medication, and bilateral subthalamic nucleus deep brain stimulation (STN-DBS) improve repetitive movements performed at low rates. When the pacing rate is increased to frequencies near 2 Hz and above, both external pacing cues and Parkinson's medication were shown to be ineffective at improving repetitive finger movement performance. It remains unclear if STN-DBS improves the performance of repetitive finger movements at high pacing rates. This study examined the effects of STN-DBS on the amplitude and rate of repetitive finger movement across a range of external pacing rates. Nine participants with STN-DBS (OFF and ON stimulation) and nine matched healthy adults performed repetitive index finger flexion movements paced by an acoustic tone that increased from 1.0 to 3.0 Hz. OFF stimulation, most subjects moved at rates that were substantially higher (hastening pattern) or lower (bradykinesia pattern) than the tone rate, particularly at high pacing rates. ON stimulation, movement rate improved in subjects with the bradykinesia pattern, but not in those with the hastening pattern. Overall, STN-DBS did not significantly affect movement rate. In contrast, STN-DBS significantly ($p < 0.05$) improved movement amplitude across all pacing rates. These findings demonstrate that STN-DBS improves movement amplitude, but had no effect on the rate of movement in participants with a hastening pattern. Separately testing movement amplitude and movement rate using both high and low rate externally paced cues in the clinical environment may aid in the diagnosis and treatment of people with Parkinson's disease.

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Keywords

STN-DBS; movement amplitude; movement rate; repetitive finger movement

Introduction

People with Parkinson's disease (PD) have marked impairments in the performance of repetitive movements which contribute to difficulties performing many activities of daily living. The clinical and functional importance of this movement type is reflected by the fact that 30% of the motor score from the Unified Parkinson's Disease Rating Scale (UPDRS) is derived from assessment of repetitive movements. During clinical testing of repetitive movements, patients are usually asked to move "as fast and as wide as possible". These instructions often result in two different behaviors: 1) low rate, large amplitude movements (bradykinetic pattern) or 2) high rate, small amplitude movements (hypokinesia or hastening pattern) [4]. The provision of external pacing cues has been proposed as a method to improve the performance of repetitive movements in people with PD [5, 10, 13]. Consistent with this idea, several studies have shown that amplitude, rate and inter-movement variability of movements are significantly improved by external pacing cues when the pacing rate is relatively slow (e.g. less than 2 Hz) [20, 28]. Yet, when movements are paced by cues presented at high rates (typically near or above 2 Hz) the impairments in repetitive finger movement worsen [6, 16, 19, 20, 23, 28]. Moreover, it has been shown that impairments in repetitive finger movement at high pacing rates are not improved with optimal medication [20, 23] and are not due to peripheral fatigue [22]. This may suggest the involvement of non-dopaminergic systems in the control of externally cued, high rate repetitive finger movements.

Examining the effects of STN-DBS on repetitive finger movements may provide further insight into the control of high rate, externally paced repetitive movement. Despite compelling evidence that STN-DBS improves clinical ratings of motor function [7], the impact of STN-DBS on repetitive movement performance remains unclear. Significant changes in self-paced finger tapping, pegboard and sequential movement tasks have been reported with STN-DBS [2, 9, 15] with improvements ranging from very modest [2] up to 75% [9, 15]. Several studies have provided evidence that STN-DBS improves the maximum amplitude and rate of proximal arm movements, but not repetitive movements of the index finger [27, 29] suggesting that STN-DBS may be less effective at improving distal than proximal repetitive movements. However, since the movements examined in these studies were self-paced, subjects used a strategy whereby movements were performed at low rates. To date, no study has examined the effects of STN-DBS on repetitive finger movements paced by external cues delivered at both low and high rates in people with PD.

The purpose of this study was to examine the effects of STN-DBS across a range of externally paced rates. We hypothesized that 1) in the OFF stimulation state, participants with STN-DBS would demonstrate a significant decrease in movement amplitude and increase in movement rate at or above pacing rates near 2 Hz and 2) movement amplitude

and movement rate at or above pacing rates near 2 Hz would not be improved with the stimulators turned ON.

Methods

Subjects

Nine participants with bilateral STN-DBS (6 male/3 female, mean age = 54 ± 11 , 6 right handed/3 left handed) were tested after a 12-hour withdrawal from all parkinsonian medication's. Nine age-, gender-, and handedness-matched healthy older adults (HOA) (6 male, 3 female, mean age = 59 ± 12 , 6 right handed/3 left handed) were also tested. Participants with STN-DBS were tested one hour after the stimulators were turned off (mean UPDRS score OFF stimulation = 44 ± 10) and one hour after the stimulators were turned on during the same day (mean UPDRS score ON stimulation = 27 ± 9). All subjects gave their written informed consent prior to inclusion into the study, and the Institutional Review Board of Northwestern University approved the procedures.

Data Collection

Participants completed an incremental frequency task, performing a finger flexion-extension movement synchronized with an acoustic tone for approximately 90 seconds [11, 23] (Figure 1). A tone was initially presented at a pacing rate of 1 Hz and then increased by 0.25 Hz until reaching 3.0 Hz. Fifteen intervals were presented for each of the nine pacing rates. The forearm, wrist, hand, thumb, and fingers 2-4 were supported with a brace maintaining the forearm in a pronated position with the elbow flexed at 90 degrees. The index finger remained unconstrained to allow for full range of motion without tactile feedback (i.e. no thumb contact). An accelerometer (Measurement Specialties EGAXT3-15-/L2M) was placed on the index finger between the first and second joints. Participants with STN-DBS used their most affected hand and HOAs used the matched counterpart. Three participants with STN-DBS and three HOAs completed the task with their non-dominant hand. HOAs completed 5 trials and participants with STN-DBS completed 5 trials in each stimulation state.

The acceleration signal was collected (Power 1401, Cambridge Electronic Design, UK; Signal 2 software, Cambridge Electronic Design, UK) and double integrated to derive finger displacement. Movement rate and peak-to-peak amplitude was calculated for each detectable movement, and then averaged across all 5 trials for each pacing rate. Both the difference and absolute value of the difference between the mean movement rate and pacing rate were calculated. Movement amplitude was normalized to data collected at 1 Hz to allow for comparisons across pacing rates and between-subjects since no constraints were placed upon range of motion.

Statistical Analyses

For all primary dependent variables (absolute movement rate difference and normalized movement amplitude), a repeated measures ANOVA was used to test for differences in the between-subjects factor of group (HOAs vs. STN-DBS OFF; HOAs vs. STB-DBS-ON) and within-subjects factor of pacing rate (1.0 to 3.0 Hz). Comparisons between the OFF and ON

STN-DBS conditions were tested separately using a repeated measures ANOVA with within subjects factors of stimulation state (OFF vs. ON) and pacing rate. Assumptions of sphericity were tested using Mauchly's Test and the degrees of freedom were corrected accordingly using Greenhouse-Geisser estimates of sphericity. Tukey's Honestly Significantly Difference Test was used for post hoc analysis of interaction effects.

Results

Data from one participant OFF and ON STN-DBS and one HOA is shown in Figure 1. Note the marked decrease in movement amplitude and increase in movement rate (hastening), when the pacing rate increased from 2 to 2.25 Hz in the OFF stimulation state. ON stimulation, this participant showed a clear improvement in movement amplitude across all pacing rates, but still hastened at pacing rates of 2.25 Hz and above. The HOA was able to perform the entire task at the required movement rate with little decrement in movement amplitude.

Figures 3A (OFF stimulation) and 3B (ON stimulation) show the mean movement rate at each pacing rate for all participants with STN-DBS. Two features of movement rate in the OFF stimulation state were noteworthy. First, 4 of 9 participants moved at a rate more than two standard deviations higher than the HOA mean rate beginning at the pacing rate of 1 Hz. Second, as the pacing rate increased, the variance in movement rate across participants increased, with a more pronounced increase at pacing rates of 2 Hz and above. The increase in movement rate variance across participants at high pacing rates reflects that hastening of movement was enhanced for some participants where as other participants showed a decline in movement rate. ON stimulation, participants that moved slower than the tone rate in the OFF stimulation state increased movement rate towards the normative range, while those who had hastened in the OFF stimulation state continued to move at rates that exceeded the normative range. The dichotomy in the behavior at higher pacing rates and corresponding increase in inter-subject variance in the STN-DBS OFF state precluded the possibility of observing significant differences in movement rate between this group and the HOA group. For this reason, we examined the error in movement rate across groups by analyzing the absolute value of the difference between the movement and pacing rate (Figure 3C). This analysis revealed significant main effects of pacing rate ($F(8) = 3.71$, $p = 0.001$, $ES = 0.19$) and group ($F(1) = 11.19$, $p = 0.004$, $ES = 0.41$) for the OFF stimulation versus HOA comparison. For the ON stimulation versus HOA comparison there was no significant main effect of pacing rate, but there was a main effect of group ($F(1) = 10.04$, $p = 0.006$, $ES = 0.39$). There were no significant interaction effects for either comparison. Comparisons between the OFF versus ON state showed a main effect of pacing rate ($F(8) = 2.36$, $p = 0.03$, $ES = 0.23$), but no group or interaction effects.

Analysis of movement amplitude data revealed main effects of pacing rate ($F(8) = 13.18$, $p < 0.001$, $ES = 0.45$), group ($F(2) = 8.89$, $p = 0.009$, $ES = 0.36$) and an interaction effect ($F(8) = 3.28$, $p = 0.02$, $ES = 0.17$) for the OFF stimulation versus HOA comparison. Post-hoc analysis revealed significant differences between groups at tone rates of 2.75 and 3.0 Hz ($p < 0.05$) (Figure 3D). For the ON stimulation versus HOA comparison, a main effect of pacing rate was found ($F(8) = 3.42$, $p = 0.001$, $ES = 0.18$) but there were no group or

interaction effects. Comparison between OFF versus ON state revealed significant main effects of pacing rate ($F(8) = 7.70$, $p < 0.001$, $ES = 0.49$), group ($F(1) = 5.13$, $p = 0.05$, $ES = 0.39$) and an interaction effect ($F(8) = 3.38$, $p = 0.003$, $ES = 0.30$). Post-hoc analysis showed no significant differences between OFF and ON stimulation across pacing rates.

Discussion

STN-DBS significantly improved the amplitude of repetitive index finger movements but not hastening at high externally paced rates. In the current study, movement rate abnormalities were most marked at rates near 2 Hz and above which is in keeping with previous studies [16, 23]. However, some participants showed an abnormal increase in movement rate at tone rates as low as 1 Hz that persisted in the ON stimulation state. In our previous study, all participants had mild-to-moderate PD and were capable of maintaining the rate and phase of movements at tone rates below 1.75 Hz [23]. The cohort of subjects in the current study had higher scores on the motor section of the UPDRS and the initial movement amplitude at tone rates of 1 Hz in this group was consistent with the “very low” amplitude categorization described by Es pay and colleagues [4]. These findings suggest that with increased severity of disease, the movement rate at which movement impairment becomes exacerbated may be markedly lowered.

Previous studies have shown that STN-DBS (in the off-medication state) significantly improved maximum amplitude and rate of diadochokinesia (forearm pronation/supination), but did not significantly improve either parameter for finger movements [29]. Inspection of the data, however, shows a marked increase in maximum finger movement rate (near 5 Hz) and a modest increase in maximum amplitude. Moreover, movements were self-paced and the primary dependent variables were derived from measures of peak rate and amplitude when performed as “fast and smoothly as possible” [29]. The high peak rates must be interpreted with caution since they might represent hastening rather than a voluntary maintenance of oscillatory movement. Similarly, average movement rates and amplitudes presented in the current study reflect a mixture of periods of hastening and slower rate movements that were in- and out-of-phase with the tone. Nonetheless, the use of the protocol in this study, where required movement rate is controlled, may aid in the examination of treatment effects. It remains to be seen which movement paradigms and associated dependent variables best correlate with impairments in activities of daily living that require repetitive movement.

Given that the task used in this study required participants to continuously move for approximately 90 seconds, the impairments noted at rates near to or above 2 Hz (approximately 50 seconds into the task) may be the result of impaired force production and timing. Previous studies have shown a decay over time in maximal or submaximal force during isometric contractions of the upper limb, delays in force rise time, and prolonged EMG relaxation times in people with PD [3, 12, 24, 30]. These delays and decay in force production may contribute to the inability to produce rapid contractions required for fast repetitive movements in persons with PD [3]. However, a recent study using the same paradigm as in this study has shown that there was no difference in maximum force production prior to and after completing the task in participants with PD off and on optimal

medication [22]. This finding suggests that the changes in movement performance during the task used in this study were not due to peripheral fatigue. However, evidence showing that STN-DBS significantly improves the rate and magnitude of force production in the off medication state [1] suggests that the improvements in movement amplitude observed in this study may have been mediated by changes in the capacity to produce force. Future research is needed to better understand the contribution of changes in force production and timing to the differential effect on movement amplitude and rate during repetitive finger movements in persons with STN-DBS.

In many patients with PD, attempts to move at high rates are associated with a marked decrease in movement amplitude, paroxysmal increase in movement rate (hastening) and an increase in the incidence and duration of hesitations of movement [16, 23]. A similar pattern of amplitude and movement rate change occurs during repetitive syllable vocalization (oral festination) [14] and the “trembling of the knees” that characterizes the festination of gait in patients with PD who have freezing episodes [18]. Nieuwboer and colleagues [17, 28] have provided evidence showing that hastening, hesitation and arrest of repetitive finger movements are more prevalent in patients with freezing gait than those without freezing gait. Based on these findings, we posit that the decrease in amplitude and hastening of repetitive movement at high pacing rates reported in this and our previous study may represent a similar type of festination behavior [17]. Consistent with this idea, speech dysarthria and freezing of gait are less responsive to dopaminergic medication and may worsen with STN-DBS [21, 25]. The lack of effect of Parkinson’s medication on the festination behavior of repetitive finger movements [23] coupled with the lack of effect of STN-DBS on hastening in this study may further support the theory that movement festination can manifest across the body axis and may reflect a distinct phenotype of PD [17, 21]. However, it remains unclear if festination/hastening is triggered by a reduction in movement amplitude, increase in movement rate or both, since both variables are inversely related [17].

In keeping with previous studies [4], not all participants in this study demonstrated hastening of repetitive finger movements. Some participants with STN-DBS moved at a rate slower than the pacing tone at rates near 2 Hz and above when OFF stimulation. These participants showed an increase in movement rate to within the normative range when ON stimulation. In contrast, those participants with STN-DBS that hastened OFF stimulation continued to hasten ON stimulation. Thus, differing PD etiologies may contribute to differing impairments in repetitive finger movements.

The significant improvement in movement amplitude observed with STN-DBS contrasts with our previous study using the same protocol that showed no improvement with optimal medication in movement rate or amplitude in people with mild-to-moderate PD [23]. These results suggest that disruption of the basal-ganglia thalamocortical pathway improves the gain/scaling of repetitive movements, but much like exogenous dopamine, does not improve the hastening of finger movements. Taken together, these findings may provide evidence that the festination-like behavior of distal upper limb movements that often emerges when patients attempt to move at higher rates is mediated by mechanisms largely independent of the nigro-striatal dopaminergic system and basal-ganglia output pathway, and that these mechanisms may regulate the control of higher movement rates.

Limitations

Hastening of finger movements at the high pacing rates may be attributed to the emergence of tremor[11]. The participants in this study had little or no evidence of resting or postural tremor. However, this criterion does not exclude the possibility that they had sub-clinical tremor that emerged during the task. Tremor is still unlikely to explain the hastening since STN-DBS typically results in a marked suppression of tremor [26]. If hastening observed at high pacing rates in the OFF stimulation state was indeed due to tremor, then a significant improvement in the ON stimulation state would be expected. The results shown in Figure 2A and B show that this did not occur. The lack of a significant change in hastening with STN-DBS may have been due to the low change in motor UPDRS scores ($36.5\% \pm 12\%$) for participants in this study compared to previous STN-DBS studies.[8]. As previously noted, the current implementation of the UPDRS instructs patients to move “as fast and wide as possible”. This instruction often requires a trade-off be made between rate and amplitude since in many patients, large amplitude movement cannot be produced at higher movement rates. This biases performance towards a large amplitude, low movement rate strategy that often results in lower UPDRS scores. By not constraining the required movement rate, movement hesitation that may emerge at higher rates may not be observed [23].

Conclusion

In conclusion, STN-DBS improves the amplitude, but not the hastening, of paced repetitive finger movements. This finding differs from the effects of optimal medication which does not significantly improve either parameter at pacing rates near to or above 2 Hz. This may suggest that impairments in movement rate of repetitive finger movements performed at high pacing rates are mediated by mechanisms largely independent of the nigro-striatal dopaminergic system and basal-ganglia output pathway. In contrast, the disruption of basal-ganglia thalamocortical pathway improves the gain/scaling of repetitive movements. These data further emphasize the need to separately test movement amplitude and movement rate across low and high pacing rates in the clinical environment, which may aid in the diagnosis and treatment of people with PD.

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Abbreviations

STN-DBS	subthalamic nucleus deep brain stimulation
STN	subthalamic nucleus
PD	Parkinson’s disease
UPDRS	Unified Parkinson’s Disease Rating Scale
HOA	healthy older adult

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Highlights

- We examined the effects of STN-DBS on repetitive finger movements.
- Subjects moved faster or slower than the tone rate off stimulation.
- STN-DBS improved movement rate in subjects who moved slower only.
- STN-DBS improved movement amplitude across all subjects.

FIG. 1.

Displacement data for one participant in the STN-DBS OFF and ON state and one HOA.

The timing of the tones is shown in the lower plot.

FIG 2.

Movement rate (movements/second) across all tone rates for all participants in the STN-DBS OFF (A) and (B) ON states. The solid line and dotted lines show the mean ± 1 STD movement rate in the HOA group. (C) Absolute value of the movement rate difference (movement rate – tone rate). (D) Average normalized peak-to-peak movement amplitude. Data represent mean $\pm$ SE in (C) and (D).