Pace of movement: the role of single neurons in the subthalamic nucleus

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OBJECTIVE The ability to modulate the pace of movement is a critical factor in the smooth operation of the motor system. The authors recently described distinct and overlapping representations of movement kinematics in the subthalamic nucleus (STN), but it is still unclear how movement pace is modulated according to the demands of the task at the neuronal level in this area. The goal of this study was to clarify how different movement paces are being controlled by neurons in the STN.

METHODS The authors performed direct recording of the electrical activity of single neurons in the STN of neurosurgical patients with Parkinson's disease undergoing implantation of a deep brain stimulator under local anesthesia while the patients performed repetitive foot and hand movements intraoperatively at multiple paces.

RESULTS A change was observed in the neuronal population controlling the movement for each pace. The mechanism for switching between these controlling populations differs for hand and foot movements.

CONCLUSIONS These findings suggest that disparate schemes are utilized in the STN for neuronal recruitment for motor control of the upper and lower extremities. The results indicate a distributed model of motor control within the STN, where the active neuronal population changes when modifying the task condition and pace.

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KEYWORDS movement pace; single-unit recording; neuronal recruitment; hands and feet motor control; subthalamic nucleus; Parkinson's disease; functional neurosurgery

HUMANS utilize their lower and upper extremities in completely different manners. Although the human motor control networks for the feet and hands share multiple brain areas, such as the primary and supplementary motor areas, premotor cortex, and subthalamic nucleus (STN),[29] physiological network differences have been described at the subregion level, such as the somatotopic organization of the STN,[17,20,25] with active movements of the wrist, arm, shoulder, leg, and foot, where the arm is represented more laterally than the leg. Our study examines differences between lower- and upper-extremity representations in the STN.

In the intact monkey, the activity of over half the cells examined in the STN was modulated in response to passive movements of individual contralateral body parts,[30] mostly to passive joint rotation produced by muscle palpation, but in some cases also in response to light touch. Within the rostrodorsal zone, a lateral region was found to contain neurons that responded to arm movements; a more medial region, to leg movement; and more dorsally and rostrally, to orofacial movements. In humans with Parkinson's disease (PD), a motor area related to passive movements was found in the dorsolateral part of the STN, with leg-related cells located medially and centrally and arm-related cells found more diffusely.[27] Responses to active and passive movements (e.g., clenching the fist, pointing, foot tapping, horizontal and vertical saccades, jaw movement, and tongue protrusion) were also demonstrated in the STN of patients with PD.[10]

Subthalamic neuronal activity has been related to mul-

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tiple motor parameters of both upper and lower extremities. Upper-extremity motor execution, motor inhibition, and error monitoring have been found to activate 3 subpopulations of subthalamic neurons,[2,3] as has Parkinsonian tremor.[1,20] Upper-extremity parameters include grip force,[18] movement onset, and movement direction.[7] Participation of the STN in lower-extremity control was shown by stimulation studies in which stimulation improved gait and postural symptoms of PD, sometimes to an almost normal level[4,11,13] (see Piper et al.[19] for a review). STN stimulation, combined with levodopa, improved gait speed, reduced gait variability (enhanced stability), and yielded lower (better) Unified Parkinson's Disease Rating Scale (UPDRS) scores.[8] We have recently shown that the STN encodes the kinematic parameters of movement—orientation, angular velocity, and acceleration—and is involved in motor coordination.[25] These findings demonstrate that the STN is a key region in the regulation of both upper- and lower-extremity movement control.

Despite the aforementioned literature, the question of how subthalamic neurons are recruited for motor control of the hand and feet is still unclear. In particular, it is not yet clear whether different paces of movement involve the same population of controlling neurons or require recruitment of additional units or whether firing modulation by itself can explain the change in movement pace. We hypothesize that a drastic change in movement pace is usually not a reflection of mere performance of the same movement slower or faster, but commonly reflects a change to the "nature" of movement, for example, from gross to fine motor skills. We therefore expect different neuronal populations to control the different paces. Here, we extend our previous study[25] by exploring this issue at the single cell level of the STN.

As deep brain stimulation (DBS) is a surgical treatment for the motor signs of PD, we believe that characterizing the physiology of the various motor-related neuronal populations is a first step that will, in the future, inform better fitting of the treatment to the signs of the disease of the individual patient and avoid side effects to neighboring populations in more focused DBS procedures.

Methods

Patients and Electrophysiology

Participants in this study were 10 patients with PD who were undergoing implantation of DBS electrodes for clinical reasons. The patients' mean age was 59.2 years (SD 11.7 years), and their mean duration of PD was 11.1 years (SD 4.2 years). All were right-handed, and 8 were male. The clinical procedure and microelectrode recordings were previously described[25] and so was spike sorting.[26] All studies were approved by the institutional review board of Tel Aviv Medical Center and conformed to its guidelines. All patients provided written informed consent.

Experimental Paradigms

Intraoperatively, patients performed unipedal and bipedal (alternating) tapping against a surface, and similarly, unimanual and bimanual (alternating) tapping, also against a surface. Although tapping, even if alternating, does not necessarily reflect gait, the intraoperative supine position constrains the task, and this setup was used as a rough approximation.

Each type of tapping was repeated at 3 internally generated paces: patient self-selected ("normal"), slow, and fast paces. Patients were first instructed to perform the tapping task. By intention, the instructions did not refer to any pace. The patients selected the pace by themselves, and none of them asked about it. Next, patients were instructed to perform the task faster than before. Finally, they were asked to perform the task slower than in the first part. During the tasks, patients wore small, light, wireless measurement devices on both wrists and the dorsal surfaces of both feet (Opal monitors; APDM Inc.). These devices recorded kinematics (acceleration, angular velocity, and orientation) in synchrony with the neuronal recording.

Data Analysis

The modeling of the firing rate function as a linear combination of each triaxial kinematic parameter—orientation, angular velocity, and acceleration (cross-validated linear regression)—and the evaluation of the nonlinear relations between firing and kinematics based on entropy correlation coefficients[28] were described in our previous study.[25] The entropy correlation coefficient is independent of the length of the time series, thus "normalizing" the longer duration of slower movements. Hence, the entropy correlation coefficient of long time series can be directly compared with those obtained from shorter series. Because the distribution of entropy correlation coefficients is not normal, the Mack-Skillings test[14] served for nonparametric 2-way unbalanced analysis of variance (ANOVA).

For large samples, the sampling distribution of the median is approximately normal. Therefore, when comparing the median entropy correlation coefficients between 2 conditions (e.g., normal-pace movements and slow movements), we employed the parametric paired-sample t-test. The same statistical test served to compare the average percentage of task-related units (over all patients) between conditions.

Results

We recorded the activity of 89 single units in the STN of 10 PD patients who were undergoing implantation of a deep brain stimulator for treatment of their motor symptoms. Figure 1 compares the average cycle times of the repetitive movements at the different paces. The figure demonstrates that the cycle time of the repetitive movements was indeed significantly different during the slow, normal, and fast tapping paces (Fig. 1A and B). This was the case independent of the limb or limbs participating in the movement. Moreover, it appears that for each tapping pace, patients selected similar cycle times for tapping with the hands as with their feet (Fig. 1C).

In our earlier work,[25] we found that in 43% (38/89) of the recorded units, the correlation between the firing rate and its kinematics-based linear estimator was significant, explaining a considerable percentage of the variance ($r^2 > 0.30$). In addition, we found significant relations between
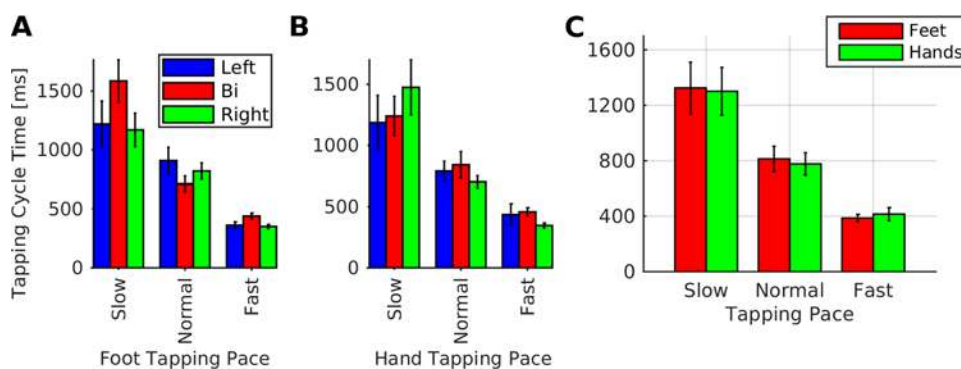
FIG. 1. Limb movement behavior in each experimental condition. The average tapping cycle time was significantly longer in the slow tapping pace than in the normal pace and significantly longer in the normal pace than in the fast condition, independent of the limb(s) involved, as expected (2 paired-sample t-tests, p < 0.05 in all tests). **A:** Foot tapping. **B:** Hand tapping. **C:** Average cycle time for the slow, normal, and fast tapping paces, for foot (*red*) and hand (*green*) movements. The pace of feet and hand movements was similar. Bi = bipedal or bimanual; ms = milliseconds. *Error bars* indicate standard errors (SEs).

kinematics and spiking activity in 93% (83/89) of recorded STN units based on the entropy correlation coefficient (see *Methods*).

In the present study, we found that the entropy correlation coefficient was significantly affected by both the tapping pace (i.e., slow, normal, or fast) and the limb (ipsi- vs contralateral) during both foot movements (pace: p < 0.0001; limb: p < 0.0001; the Mack-Skillings test for nonparametric 2-way unbalanced ANOVA) and hand movements (pace: p < 0.0001; limb: p < 0.0001; Fig. 2A and B). Notice, however, that independent of the limb, the entropy correlation coefficient was larger during normal-pace movements than during slow movements (see also Fig. 2C), both for hands (p = 0.017; paired-sample t-test) and for feet (p = 0.043). Thus, the recorded neurons apparently encode less information in slow movements than in normal-pace ones.

So far, we examined the change in entropy correlation coefficient for each neuron by itself. Does this mean that for both foot and hand movements the population as a whole encodes less information for slow movements than for normal-pace movements? To address this question, we examined the percentage of units recruited for the tapping task under each condition. This percentage changed as a function of movement pace, as can be seen by the stair-like structure in Fig. 2D and E. Even though this type of structure is common to hands and feet, the order of the "stairs" is different (note the different labeling of the y-axes in Fig. 2D and E). For foot movements, normal-pace movements yielded the maximum percentage of recruited units, slow movements yielded significantly less (normal > slow: p = 0.035, paired-sample t-test; see *Methods*), and fast movements yielded the least (slow > fast: p = 0.0065). In contrast, for hand movements, slow movements were the ones recruiting the maximum percentage of units; normal-pace movements, significantly less (slow > normal: p = 0.0037); and fast movements, the least (normal > fast: p = 0.0064). Thus, for foot movements, the change of pace from normal to slow results in fewer units recruited for the task (Fig. 2F, blue), each unit carrying less information on the slow movement task (Fig. 2C, blue). For hand

movements, however, each unit carried less information on the slow movements (Fig. 2C, red), but more units were recruited for the task (Fig. 2F, red).

Direct comparison of the percentage of units recruited to control hand and foot movements in each pace reveals that for the slow (p = 0.22) and fast (p = 0.51) paces there was no significant difference between the upper and lower limbs. However, as Fig. 2F shows, during normal pace, the difference between feet and hands was significant (p = 0.001; feet > hands, paired-sample t-test). Similarly, feet and hands did not differ significantly in their entropy correlation coefficient during slow (p = 0.17) and fast (p = 0.12) paces, but they did during normal pace (p = 0.039; feet > hands, paired-sample t-test).

Discussion

In this study, we report disparate pace-dependent recruitment schemes for subthalamic neurons controlling hand movements compared with those controlling the feet. The information encoded by the activity of each controlling neuron decreased when moving from a normal, self-selected pace to a slow tapping pace, in both lower- and upper-extremity movements (see Fig. 2A–C). For foot movements, this decrease was accompanied by a reduction in the percentage of recorded neurons recruited for the task (see Fig. 2D–F), leading to an overall reduction in the task-related information represented by the population as a whole. In contrast, for hand movements, the percentage of recruited neurons we recorded increased, in what might be a compensatory mechanism that uses more neurons, each carrying less information. Thus, the population as a whole may avoid significant reduction in the amount of information about slow movements in comparison with normal-pace ones. Slow hand movements may serve, for example, in fine motor skills, and may thus require finer control, that is, increased neuronal activity or a shift in neuronal activity between cell populations. Slow movements also result from deficits shown by the patients, including bradykinesia.
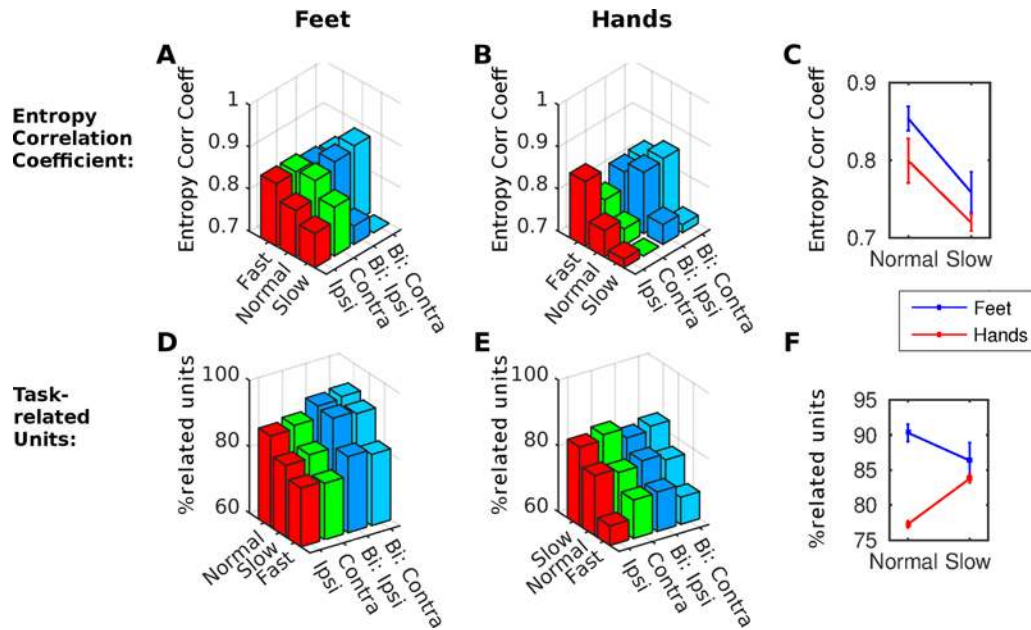
Our finding of different neuronal populations each spe-

FIG. 2. Median entropy correlation coefficient and average percentage of task-related units, over all patients, for each tapping pace and each limb. **A–C:** Entropy correlation coefficient. The median entropy correlation coefficient varied significantly with both pace and limb, for both foot (A) and hand (B) movements. Note in particular the reduction in information when moving from normal pace to slow pace, independently of the limb. This transition is summarized in C: the entropy correlation coefficient decreases for both foot (*blue*) and hand (*red*) movements. **D–F:** Percentage of task-related units. The average percentage of task-related units shows a stair-like structure. For foot tapping (D), more neurons are recruited during normal tapping, fewer during slow tapping, and even fewer during fast tapping. For hand tapping (E), slow tapping recruits the largest amount of units; normal tapping, fewer; and fast pace, the least, independent of the limb. (Note the different labeling of the pace axes in D and E.) The percentages of recruited neurons in normal and slow movements are summarized in F. Neuronal recruitment schemes differ between feet (*blue*) and hand (*red*) movements. For foot movements, the transition decreases the amount of participating neurons. Combined with the decrease in information encoded by each neuron (C), the overall result is reduced encoded information for slow foot movements. In contrast, for hand movements the decrease in encoded information (C) is compensated for by recruiting more neurons for the task (increase in percentage of recruited neurons). Bi = bipedal or bimanual; coeff = coefficient; contra = contralateral; corr = correlation; ipsi = ipsilateral.

cifically involved in a certain pace of movement extends existing evidence in the mouse spinal cord, where ablation of inhibitory V0 neurons leads to a quadrupedal hopping at all frequencies of locomotion, but with a differential effect at different locomotor frequencies: lack of left-right pattern at low frequencies, mixed coordination at medium frequencies, and left-right alternation at high locomotor frequencies.[22] Similarly, switches in spinal circuits during increases in locomotor speed were provided by studies of swimming in larval zebrafish.[12]

The aforementioned differences in the neuronal recruitment scheme between foot and hand movements cannot be explained by differences in tapping paces, as the average pace of foot movements was similar to that of hand movements (Fig. 1). The recruitment differences are, however, consistent with existing evidence for the role of the STN in the control of automatic behavior[9] and task switching,[15] because automatic behavior most closely reflects movements in the normal, patient-selected pace. As we have shown, for this type of movement the STN encodes more kinematic information than for slow movements, implying greater subthalamic involvement in the control of automatic movements. Moreover, the reported differences also suggest that an external electrical stimulation to the STN

will likely yield distinct effects at each movement pace. This may thus indirectly explain, at the single cell level, the differences in step length and velocity induced by DBS in normal-pace versus fast gait.[4]

The difference in percentage of recruited units for hand and foot movements is about 12% (Fig. 2F, normal pace). This percentage is similar to percentages reported in the literature on human neurophysiology to describe various phenomena—for example, units related to speech in the temporal and frontal lobes[24] (8%, 49 units), visuomotor units in the parahippocampal gyrus[23] (9%, 11 units), or pure bipedal units in the STN[25] (11%, 10 units). We therefore conclude that disparate pace-dependent recruitment schemes exist for the STN neurons that control hand and foot movements.

Understanding the neuronal recruitment schemes for different types of movements (e.g., different paces) may, in the future, assist neurosurgeons in the optimal targeting of DBS electrodes to achieve multiple goals. First, it may help in targeting areas with neuronal activity related to specific symptoms, for example, slow gait. Second, it may assist in avoiding DBS side effects, such as the aforementioned difference in the influence of stimulation on fast versus normal paces. Third, more focused stimulation may

be developed that will combine the two benefits: it will target a specific group of neurons to treat a specific symptom while avoiding other neurons that, when stimulated unnecessarily, produce side effects. Fourth, closed-loop DBS[21] may be tailored for different types of movement based on the different neuronal populations identified.

Our results suggest that different movement paces may lead to distinct motor control schemes in the STN, as opposed to a single control scheme that takes velocity or pace into account, as is the case, for example, in the primary motor cortex.[5,6,16] Nevertheless, as we recorded from a random sample of cells, and as the size of the sample is small relative to the whole neuronal population that controls movement within the STN, we must bear in mind that the distinct schemes that we observed may in fact represent different aspects of a more complex unified scheme. Future research with a larger cohort may be necessary for a more complete understanding of the underlying mechanisms.

Conclusions

Change of pace of movement is achieved by recruitment of the corresponding subthalamic neuronal population. The recruitment schemes for controlling hand movements differ from those for controlling the feet. Our findings are thus an important step on the way to deciphering the neuronal mechanisms involved in the recruitment of subthalamic neurons for the motor control task. In the future, these results may help to facilitate more focused implantation of DBS electrodes in patients with movement disorders, targeting specific symptoms related to movement kinematics.

Acknowledgments

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Disclosures

Dr. Giladi reports a consultant relationship with Teva-Lundbeck, Intec Pharma, NeuroDerm, Armon Neuromedical Ltd., Dexcel, Pharma Two B, UCB, Lysosomal Therapeutics Inc. (LTI), and Montfort; direct stock ownership in LTI; and membership on advisory boards of Teva-Lundbeck, LTI, Dexcel, AbbVie, NeuroDerm, and Sionara Mont4.

Author Contributions

Conception and design: all authors. Acquisition of data: Tankus, Fried. Analysis and interpretation of data: Tankus, Giladi, Hausdorff. Drafting the article: Tankus, Hausdorff. Critically revising the article: all authors. Reviewed submitted version of manuscript: Tankus. Statistical analysis: Tankus.

Supplemental Information

Previous Presentations

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