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Spinal Cord Stimulation Restores Locomotion in Animal Models of Parkinson's disease¹

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Abstract

Dopamine replacement therapy is useful for treating motor symptoms in the early phase of Parkinson's disease, but is less effective in the long-term. Electrical deep-brain stimulation is a valuable complement to pharmacological treatment but involves a highly invasive surgical procedure. We found that epidural electrical stimulation of the dorsal columns in the spinal cord restores locomotion in both acute pharmacologically induced dopamine-depleted mice and in chronic 6-hydroxydopamine lesioned rats. The functional recovery was paralleled by a disruption of aberrant low-frequency synchronous corticostriatal oscillations, leading to the emergence of neuronal activity patterns that resemble the state normally preceding spontaneous initiation of locomotion. We propose that dorsal column stimulation might become an efficient and less invasive alternative for treatment of Parkinson's disease in the future.

Patients suffering from Parkinson's disease (PD) experience chronic and progressive motor impairment (1). The main cause of PD is basal ganglia dysfunction, resulting from degeneration of neurons in the dopaminergic nigrostriatal pathway (2). Dopamine replacement therapy, through administration of the dopamine precursor 3,4-dihydroxy-L-phenylalanine (L-DOPA), effectively ameliorates symptoms associated with PD, and remains the treatment of choice to date (3). Unfortunately, L-DOPA pharmacotherapy has proven less efficient in the long-term and is associated with several complications (4). Additional therapeutic strategies, employed in conjunction with pharmacological treatment, have thus attracted considerable attention. In particular, improved techniques for electrical stimulation of the basal ganglia — referred to as deep-brain stimulation (DBS) - are effective for treatment of motor symptoms in PD (5).

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Supporting Online Material www.sciencemag.org Material and Methods Figs. S1, S2, S3, S4, S5, S6, S7, S8, S9 Movie S1

ONE SENTENCE SUMMARY: We show that epidural electrical stimulation of the dorsal column pathways produces specific shifts in neuronal activity patterns in corticostriatal circuits and causes a dramatic recovery of locomotive ability in both acute and chronic animal models of Parkinson's disease.

Furthermore, DBS permits a reduction of L-DOPA dosage in PD patients (6). However, a disadvantage of DBS is the requirement of a highly invasive surgical procedure, as well as the crucial dependence on accurate targeting of very small brain structures (7). Hence, it is desirable to identify a less invasive method to electrically stimulate neuronal circuits to obtain beneficial effects similar to those of DBS.

Some clues for new PD therapies may come from epilepsy studies. In both animal models and in epilepsy patients, stimulation of peripheral nerve afferents is effective in desynchronizing aberrant low-frequency neural oscillatory activity, thereby reducing the frequency and duration of seizure episodes (8-10). Aberrant low-frequency neural oscillations are well documented in patients (11,12) and in animal models of PD (13). These findings led us to hypothesize that stimulation of afferent somatic pathways could alleviate motor symptoms of PD by disrupting aberrant low-frequency oscillations.

Dopamine, akinesia and synchrony

The first set of experiments was carried out using an inducible mouse model of PD, first in wild-type animals and then in dopamine-transporter knock-out (DAT-KO) mice (14). Through pharmacological inhibition of dopamine synthesis, we induced acute dopamine depletion in both types of animals (2,13,14). In patients, the cardinal symptoms of idiopathic PD have been reported to be clinically apparent following degeneration of 60-70% of the dopaminergic neurons of the substantia nigra pars compacta, which results in a 30-50% reduction of striatal dopamine levels (15,16). We achieved acute pharmacological dopamine depletion slightly below the levels observed in PD patients (69% reduction of striatal dopamine levels; mean $\pm$ SD = 4.5 ± 2.0 ng dopamine per mg tissue in depleted animals compared to 14.4 ± 3.3 in controls; $p < 0.005$ Mann-Whitney, $n = 6/6$, fig. S1) in wild-type C57/BL6J mice with two i.p. injections (250 mg/kg) of the tyrosine hydroxylase inhibitor *alpha-methyl-para-tyrosine* (AMPT) during a 6 h period (15,16). Equivalent symptoms of main clinical motor manifestations in PD patients were found in AMPT-injected mice (Fig. S2 and S3). In particular, locomotive activity was significantly reduced [average locomotion scores in non-depleted and depleted animals were (mean $\pm$ SEM) 3.7 ± 0.1 and 0.4 ± 0.02 mm/s, $n = 11$ and 14, respectively] and a preferential reduction of faster movements indicated bradykinesia in the depleted state (Fig. S2, see also (17) and (18)).

Neuronal activity patterns of dorsolateral striatum and primary motor cortex (MI) were also significantly altered. Differences were found both on the population level, through inspection of local field potentials (LFP), and in the firing patterns of single cortical and striatal neurons (13). Fig. 1A shows an example of LFP spectrograms recorded in MI during two 5-min periods before and after dopamine depletion (second and third rows, left and right, respectively). Spectral analysis revealed particularly powerful oscillations around 1.5–4 Hz and in the lower beta range (10–15 Hz), whereas the power of oscillations >25 Hz was decreased in relation to baseline conditions (standardized spectrograms, Fig. 1A, third and fourth row; see also Fig. S6).

Important differences in single- and multi-unit activity were also found. The firing rates of a majority of 52 striatal and cortical neurons, which were positively identified after a 6 hour depletion period, showed significant differences (70.0 % in motor cortex and 75.0% in striatum, $\alpha = 0.001$) when we compared the more active non-depleted state and the immobile depleted condition (see activity raster plots shown for a few units in Fig. 1A, bottom row). During dopamine depletion, a higher proportion of neurons tended to discharge phase-locked to LFP oscillation, in effect resulting in increased synchronicity (52.7% [64/129] in depleted vs. 37.0% [44/127] in non-depleted state; $\alpha = 0.001$; for details see Fig. S6).

DCS alleviates akinesia and synchrony

The effect of dorsal column stimulation (DCS) was next evaluated in mice before and after acute pharmacological dopamine depletion. DCS was achieved by chronic implantation of custom-made flat bipolar platinum electrodes positioned epidurally above the dorsal columns of the spinal cord at the upper thoracic level (Fig. 1 B, C).

DCS had a dramatic effect on the amount of locomotion displayed during stimulation periods in the dopamine-depleted animals. This effect was strongest for 300 Hz stimulation; on average the amount of locomotion during stimulation periods was more than 26 times higher than during the 5 minute period prior to stimulation (Fig. 2A, see also Movie S1). DCS had a smaller, albeit clear effect, using lower stimulation frequencies. In contrast, control experiments using air-puffs or trigeminal nerve stimulation were not effective (Fig. 2A and Fig. S5). DCS caused increased locomotion also during non-depleted conditions, but this increase was moderate (4.9 times pre-stimulus values at 300 Hz) in comparison to that in depleted animals (Fig. 2A). Locomotion was normally initiated a few seconds after the onset of DCS, with a slightly longer delay in depleted animals (median = 3.35/1.35 s, interquartile range = 2.22/1.22 s, $p = 0.023$, Mann-Whitey, in depleted/non-depleted animals, at 300 Hz). In addition, a small residual effect was found after high-frequency stimulation in depleted, but not in non-depleted animals (3.4 and 0.95 times pre-stimulus values, respectively for during the 30 s following 300 Hz DCS). DCS also proved efficient for alleviation of bradykinesia as indicated by the relatively larger increase in the amount of fast movement components in depleted animals (Fig. 2B).

Analysis of LFP recordings during DCS in both MI and in striatum showed a shift in spectral power from lower to higher frequencies (average spectrograms from a total of 21 events of DCS at 300 Hz obtained from 9 animals are shown in Fig. 2C). The spectral shift was maintained throughout the stimulation period and lasted for ~50 s following the off-set of stimulation. To condense the spectral shift into a single measure, a spectral index was computed by dividing the spectral range analyzed into an upper and lower half and calculating the ratio of the summed power of the frequencies in the two intervals [(25-55Hz)/(1.5-25Hz)]. The spectral index (black trace in Fig. 2C) illustrates the rapid spectral shift induced by DCS and the prolonged effect after DCS had ceased.

DCS also affected the firing patterns of individual neurons. To avoid interference from stimulation artifacts, the 30 second stimulation periods were excluded from the analysis of spike data. But even during the period following stimulation, numerous neurons showed significantly altered firing rates (47.9% in MI and 41.8% in striatum, $\alpha = 0.01$; Fig. 2C, row 4 and 5, respectively). The fraction of units entrained to LFP dropped notably (from 42.7/38.8 % in MI/striatum the 30 s before DCS to 24.5/24.0 % the 30 s after DCS, $\alpha = 0.01$).

Although the onset of locomotion was delayed a few seconds, changes in the neural activity were detected almost immediately following DCS onset (mean $\pm$ SD evoked potential latency = 44 ± 5 ms), perhaps indicating that the electrophysiological changes have a permissive rather than directly instructive role for the initiation of locomotion.

A brain state permissive of locomotion

During the relatively rare instances when the depleted animals displayed locomotion, low-frequency oscillations were diminished (Fig. 1A). This situation bears an obvious resemblance to the DCS induced state. Thus, a certain decrease of low-frequency oscillations may be required to initiate locomotion. We analyzed the detailed temporal patterns of shifts in oscillatory LFP activity during spontaneous locomotion events in non-depleted (115 events in 10 animals) and depleted mice (51 events in 5 animals) (Fig. 3 A, B). In both states, significant spectral shifts assessed by spectral index changes ($p < 0.01$) (19), from lower to higher

frequencies were detected a number of seconds prior to the initiation of locomotion (non-depleted: mean $\pm$ SD = 2.9 ± 1.7 s, range 0.1–5.5 s, $n = 88$, MI and striatal LFP; depleted: 3.0 ± 1.7 , range 0.2–5.5 s, $n = 48$, MI and striatal LFP). Yet, there were also important differences, most notably below 25 Hz. A more differentiated decrease in power of oscillations below 8 Hz and an increase above 17 Hz was observed in non-depleted animals, whereas the spectral power in a broader range between 5 and 25 Hz was decreased in depleted animals. Because these different patterns occurred before the onset of locomotion, it is unlikely that they were due to differences in locomotion between the two groups. Instead, they could be part of the explanation why depleted animals moved slower and for shorter time periods.

On the single neuron level, the same type of firing rate changes after DCS also occurred in conjunction with spontaneous locomotion events. From a total pool of 193 neurons (from 9 control and 5 dopamine-depleted recordings sessions in 11 animals), 111 modulated their firing rate during locomotion and unexpectedly, 59 of these neurons showed a pattern of early activation, 2.9 ± 1.4 s (mean $\pm$ SD) before actual locomotion onset (range = 0.5–4.5 s, $n = 59$ striatal and MI units from depleted and non-depleted conditions, Fig. 3C).

DCS in combination with L-DOPA treatment

To find the minimum dose of L-DOPA (alone or combined with 300 Hz DCS) required to restore locomotion, DAT-KO mice were used. These mice have <5% of normal striatal content of dopamine (14). Dopamine can be further decreased to virtually undetectable levels by injecting AMPT (250 mg/kg i.p.) resulting in a completely akinetic animal model (14). By gradually increasing dopamine levels through repeated L-DOPA injections every hour, we tested the locomotion thresholds. In the group receiving only L-DOPA injections ($n = 6$ sessions from 4 mice), locomotion typically first occurred after the fifth injection (5 mg/kg dose, corresponding to a total dose of 15 mg during the first five hours). When L-DOPA treatment was combined with DCS, the same amount of locomotion was displayed after the second injection (2 mg/kg dose, corresponding to a total dose of 3 mg in the first two hours) ($n = 10$ experiments from 7 mice, Fig. 4A). That means that in combination with DCS, 1/5 of the L-DOPA total dose was enough to produce equivalent locomotion to L-DOPA alone. There was also a general increase in the amount of locomotion displayed in the L-DOPA+DCS group over the entire range studied. Thus, L-DOPA+DCS seems to be superior to L-DOPA alone in terms of the ability to rescue locomotive capability after severe dopamine depletion. Finally, animals in the L-DOPA+DCS group consistently showed higher values of spectral index than the L-DOPA only group. This suggests that DCS facilitates locomotion, even in severely depleted animals, through similar mechanisms (Fig. S7).

DCS is effective after chronic lesions

Although the acute dopamine depletion model employed in the first set of experiments could reproduce all the main symptoms of PD, it was important to confirm the effectiveness of DCS in an animal model that also involves loss of nigrostriatal dopaminergic connections. Chronic dopaminergic denervation of the striatum was achieved using bilateral 6-OHDA lesions in rats ($n = 4$) resulting in progressive deterioration of motor function and sustained weight loss, both cardinal signs of successful lesioning (20,21). When placed in the open-field, lesioned rats displayed reduced locomotion compared to controls ($n = 4$), which received vehicle injections in identical sites in the striatum (mean $\pm$ SEM = 2.85 ± 0.068 and 7.78 ± 0.144 mm/s on average, respectively). Quantification of immunohistochemical staining of the dopamine synthesizing enzyme tyrosine hydroxylase indicated that lesioned rats had only ~20% of the immune-signal found in sham-lesioned animals (Fig. S8).

Rats were tested during two one-hour sessions in the open-field, the first hour without stimulation and the second with DCS applied for 30 s every tenth minute. In the lesioned group, DCS resulted in remarkably increased amounts of locomotion compared to the first hour, whereas sham animals actually moved less during DCS sessions than during non-DCS sessions (Fig. 4C). Hence, there were specific improvements of motor function in the Parkinsonian state compared to controls. In lesioned rats, DCS not only alleviated hypokinesia during stimulation, but it also caused an increase in locomotion after the stimulation period. This residual effect lasted around 100 s (Fig. 4B).

The effect of DCS on bradykinesia in 6-OHDA lesioned rats was also evaluated. Lesioned animals showed a relative increase in the number of scored locomotion events for all movement speeds but this effect was more pronounced for faster movements, indicating a specific effect on bradykinetic symptoms in addition to the general improvement in the overall amount of locomotion (Fig. 4D).

Discussion

We demonstrated that stimulation of the dorsal column pathways using epidural implanted bipolar electrodes — a simple, easy to perform, semi-invasive method — can restore locomotive capability in two animal models of PD symptoms: acutely dopamine-depleted mice and rats with dopaminergic neuronal loss. In parallel with the behavioral improvements, DCS shifted activity patterns in the primary motor cortex and in the dorsolateral striatum into a state closely resembling that found prior to and during spontaneous initiation of locomotion in normal and depleted animals. This suggests that DCS helps motor related brain areas shift into a state permissive of the initiation of movements.

What could be the mechanisms through which DCS allows a shift into a locomotion permissive state? The first possible explanation could be that DCS, in addition to stimulating specific somatosensory pathways, may also recruit brainstem arousal systems, leading to sufficient cortical and striatal desynchronization required for voluntary initiation of movements (8). Such a possibility can be raised when the phenomenon of paradoxical kinesia is considered, i.e. rare events in which PD patients, aroused by frightening situations, exhibit sudden and transient improvement in motor function (22,23). Here, the 4.9 fold increase in locomotion produced by DCS in control animals, albeit much less than that observed in dopamine-depleted animals, could in theory support such an arousal hypothesis. Yet, a variety of observations suggest that this may not be the main mechanism accounting for DCS induced locomotion. Firstly, neither air-puffs alone nor stimulation of trigeminal nerve afferents, both potent somatosensory arousal stimuli, induced locomotion in either control or dopamine-depleted animals. Secondly, in control experiments carried out in both awake and lightly anesthetized animals, DCS produced only a minimal arousal response when compared to other tactile, proprioceptive, and nociceptive stimuli (Fig. S9a and b). This is in line with a previous study that demonstrated that dorsal column recruitment produces no significant arousal effect (24). Overall, these data suggest that DCS may increase locomotion behavior primarily through direct modulation of lemniscal/thalamic pathways. However, more experiments will be required to settle this issue.

Our electrophysiological data suggest possible mechanisms for the success of DCS in restoration of locomotion, based on existing theories of basal ganglia pathology in PD and specifically considering the circuitry known to be involved in initiating voluntary locomotion (25). The command to the spinal cord to initiate locomotion, via reticulospinal pathways, is issued by the diencephalic and mesencephalic locomotor regions. For these midbrain structures to become active and trigger locomotion, they must be relieved from the tonic inhibition exerted by the output nuclei of the basal ganglia. This is accomplished by activation of striatal medium spiny neurons projecting to the output nuclei of the basal ganglia (26,27). Under normal

circumstances, the cortex has a powerful excitatory influence on the striatum. In contrast, with reduced striatal dopamine levels, the activation threshold of the projection neurons from the striatum is significantly increased (25), making it less likely that cortical input to the striatum will be conveyed through this pathway. As a consequence, brainstem motor regions remain under tonic inhibition, and the initiation of goal directed locomotion and other types of volitional motor activity become impaired. DCS may exert its effect by activating large cortical areas, increasing the cortical and thalamic input to the striatum. This may in turn, promote the depolarization and, consequently, facilitate the activation of striatal projection neurons. Another consequence of the reduced cortical control of striatum at low dopamine levels is that both thalamic and internally driven striatal low-frequency oscillations become more prominent (28,29). These oscillations may lead to increased synchronicity because the generation of action potentials tends to occur at more distinct phases of the LFP oscillation (13,30). This was confirmed in our experiments in which both motor cortex and striatum showed excessive low-frequency synchronized oscillatory activity in dopamine-depleted animals and an increased entrainment of spikes to low-frequency components of the LFPs. Such synchronous activity interferes with normal information processing in these circuits and should likely be considered pathogenic in PD (12). Our data show that DCS effectively abolishes aberrant synchronous low-frequency oscillations. It is, therefore, tempting to speculate that the suppression of low-frequency oscillations is particularly important for amelioration of motor symptoms in PD (31).

Finally, the combined effect of L-DOPA and DCS allowed for recovery of motor function at significantly lower doses of L-DOPA in severely dopamine-depleted animals. The considerably less invasive nature of the epidural DCS electrode compared to DBS electrodes suggests that DCS could be a complement for treatment of symptoms of PD in earlier stages of the disease. We therefore propose that DCS should be investigated further in extensive experiments employing primate models of PD, preferably over longer time periods, to evaluate the potential viability of this new procedure as a new treatment for Parkinsonian patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Acute inhibition of dopamine synthesis produces a Parkinsonian state

(A) Examples of LFP spectrograms and firing rate plots recorded in MI during two 5-minute periods before and after dopamine depletion. Top row: locomotion during recording periods, second row: LFP power, third row: LFP power standardized to the non-depleted 5-minute period, fourth row: close-up of low-frequency range shown in third row. Note the increased power in low frequencies in the depleted state (black arrows) and the relative normalization of spectral power upon locomotion (red arrow). Bottom row: average firing per second for 6 MI units. (B) Set-up for electrical stimulation of dorsal columns: The stimulation electrode (red) is implanted above the spinal cord and connection wires are passed subcutaneously to a connector attached to the skull. Two stimulus-isolator units provide biphasic constant-current

pulses at desired frequency and intensity. (C) Schematic dorsal (left) and sagittal view (right) of the implanted electrode. *r*: rostral; *c*: caudal.

Figure 2. DCS restores locomotion and desynchronizes corticostriatal activity

(A) Relative change in amount of locomotion in depleted and non-depleted mice (DCS frequencies specified on x-axis, n.V: trigeminal nerve stimulation; mean and SD shown, means for all conditions before and after depletion are significantly different, $\alpha = 0.005$). (B) DCS preferentially increases the fraction of faster movement components in dopamine depleted animals but not in controls. (C) Average spectrograms of striatal LFPs and firing rates recorded around 300 Hz stimulation events (yellow bar), top row: LFP power (n = 21 events; black trace denotes spectral index, see main text) second row: LFP power standardized to first 240 s. Row 4 and 5, respectively: firing rate for 98 striatal and 96 cortical units (standardized to firing rates during first 240 s and ordered by responsiveness after DCS (19), n = 36 events). Neurons

exhibiting significant changes during the 30s-period following stimulation (black line) are indicated with red and blue rectangles (excitatory and inhibitory responses). Middle row: Average locomotion ($n = 36$ events).

Figure 3. Activity patterns during spontaneous locomotion

(A) Average spectrogram of striatal LFP aligned to the onset of spontaneous locomotion in control ($n = 115$ events) and dopamine-depleted condition ($n = 51$ events). The gradual shift from lower to higher frequencies indicated by the average spectral index (black trace) starts before locomotion onset (dashed white line). (B) Standardization of spectrogram relative to directly preceding non-locomotion periods (collected between 20 to 10 s prior to locomotion onset from 112 stationary 10 s periods). (C) Firing rate (binned at 0.5 s) of striatal and MI units around the onset of spontaneous locomotion. Significant changes in firing rate (as compared to stationary period) are indicated with magenta (excitatory) and blue (inhibitory response) crosses. (D) Average locomotion during recorded events.

Figure 4. DCS restores locomotion in severely dopamine-depleted mice and in chronically lesioned rats

(A) The cumulative amount of locomotion scored in animals receiving DCS in combination with successive L-DOPA injections (black) was significantly higher at all time points than what was observed for the group only receiving L-DOPA (gray). (B) DCS (yellow shaded area) induced a prominent increase in locomotion in 6-OHDA lesioned rats (shaded area around trace is SEM) compared to preceding non-DCS sessions. In the sham group, in contrast, DCS caused a moderate response comparable to non-DCS sessions (mean $\pm$ SEM, $n = 64$ stimulation and 64 control sessions for both sham treated and lesioned rats). (C) DCS specifically increases locomotion in 6-OHDA lesioned rats (mean and SEM shown; all means are significantly

different to the others, $p < 0.001$, Kruskal-Wallis and Dunn's multiple comparison test; flashes indicate DCS sessions). (**D**) A preferential relative increase of faster movement components locomotion was found in the 6-OHDA lesioned group reflecting alleviation of bradykinetic symptoms. Ratios of the sum of recorded locomotion episodes in three speed intervals [DCS/non-DCS sessions] are shown.