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Deep brain stimulation of the subthalamic or entopeduncular nucleus attenuates vacuous chewing movements in a rodent model of tardive dyskinesia

Meaghan Creed [a,d], Clement Hamani [d,e], José N. Nobrega [a,b,c,d,*]

[a] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
[b] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[c] Department of Psychology, University of Toronto, Toronto, ON, Canada
[d] Neuroimaging Research Section, Centre for Addiction and Mental Health, Toronto, ON, Canada
[e] Division of Neurosurgery, Toronto Western Hospital, Toronto, ON, Canada

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Abstract

Deep brain stimulation (DBS) has recently emerged as a potential intervention for treatment-resistant tardive dyskinesia (TD). Despite promising case reports, no consensus exists as yet regarding optimal stimulation parameters or neuroanatomical target for DBS in TD. Here we report the use of DBS in an animal model of TD. We applied DBS (100 μA) acutely to the entopeduncular nucleus (EPN) or subthalamic nucleus (STN) in rats with well established vacuous chewing movements (VCMs) induced by 12 weeks of haloperidol (HAL) treatment. Stimulation of the STN or EPN resulted in significant reductions in VCM counts at frequencies of 30, 60 or 130 Hz. In the STN DBS groups, effects were significantly more pronounced at 130 Hz than at lower frequencies, whereas at the EPN the three frequencies were equipotent. Unilateral stimulation at 130 Hz was also effective when applied to either nucleus. These results suggest that stimulation of either the EPN or STN significantly alleviates oral dyskinesias induced by chronic HAL. The chronic HAL VCM model preparation may be useful to explore mechanisms underlying DBS effects in drug-induced dyskinesias.

1. Introduction

Tardive dyskinesia (TD) is a persistent and debilitating hyperkinetic movement disorder associated with long-term treatment with classical antipsychotic drugs. Risk of developing TD increases by approximately 5% per year of treatment and constitutes a major limitation of antipsychotic therapy

* Corresponding author. Neuroimaging Research Section, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, Canada M5T 1R8. Tel.: +1 416 535 8501x6259; fax: +1 416 979 4739.
E-mail address: jose_nobrega@camh.net (J.N. Nobrega).

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(Glazer, 2000; Glazer et al., 1993). While the incidence of TD is much lower with newer atypical antipsychotics (Correll and Schenk, 2008), they carry risks of their own, including agranulocytosis, excessive weight gain, diabetes and potentially fatal metabolic complications (Haddad and Sharma, 2007). Thus classical antipsychotic medications are still used, and TD remains a significant clinical problem (Remington, 2007).

Leading hypotheses of TD etiology have proposed various roles for dopamine D2 receptor alterations (Casey, 2004; Klawans and Rubovits, 1972; Turrone et al., 2003, 2002) and/or neurotoxic mechanisms (Andreassen et al., 2003; Murata et al., 2007) involving altered glutamatergic transmission (Andreassen and Jorgensen, 2000; Burger et al., 2005; Tsai et al., 1998) possibly leading to disinhibition of basal ganglia output pathways (Albin et al., 1989; Andreassen et al., 2001). Partly in line with these hypotheses, a number of diverse pharmacological treatments have been attempted with varying degrees of efficacy on TD symptoms. In all, the management of TD remains challenging (Soares and McGrath, 1999). For patients with persistent TD that is not responsive to pharmacological treatments, there has been a resurgence of interest in deep brain stimulation (DBS) as a therapeutic intervention, following positive outcomes in other movement disorders. DBS involves local application of electric current through surgically implanted electrodes, and it has been successfully used in tens of thousands of patients with various types of movement disorders (Hamani and Moro, 2007). In the specific case of TD, recent case reports have also produced promising results (Eltahawy et al., 2004; Kefalopoulou et al., 2009; Kosel et al., 2007; Sako et al., 2008; Schrader et al., 2004). A recent prospective multicenter study using double-blind evaluation in the presence and absence of DBS also reported significant reduction of TD symptoms at 6 months in the first 10 patients treated (Damier et al., 2007).

To date DBS trials for TD have mostly focused on the internal globus pallidus (GPi) as a key basal ganglia output station (Albin et al., 1989; Damier et al., 2007). However, in the case of tardive dystonia, a condition that is also induced by chronic antipsychotic drug treatment, stimulation of the subthalamic nucleus (STN) has been suggested as an alternative (Sun et al., 2007). Indeed STN DBS has been widely used for the treatment of other movement disorders associated with basal ganglia pathology, particularly Parkinson's disease (Benabid et al., 2009; Del Sorbo and Albanese, 2008; Kitagawa et al., 2000; Murata et al., 2003). Other points of uncertainty refer to optimal stimulation parameters (e.g. frequency and intensity of stimulation) and the comparative effectiveness of unilateral vs. bilateral stimulation at different anatomical targets (Schrader et al., 2004). In this context investigating DBS effects in animal models of TD could prove particularly informative.

In several species including rats and mice, chronic treatment with haloperidol (HAL) or other first-generation antipsychotic drugs induces a well-characterized syndrome of vacuous chewing movements (VCMs), which has a number of features analogous to human TD (Tamminga et al., 1990; Turrone et al., 2002). Accordingly, the VCM model has been the most extensively studied and is currently the best characterized model of TD (Andreassen et al., 2003; Clow et al., 1980; Egan et al., 1996a,b, 1995; Gunne et al., 1982; Tamminga et al., 1990; Waddington, 1990). In the present study we assessed the effects of DBS applied to the entopeduncular nucleus (EPN, the rodent homologue of the globus pallidus internus) or the subthalamic nucleus (STN) on VCMs induced by long-term HAL treatment. We examined the efficacy of different current frequencies applied bilaterally to either anatomical target. We also compared the effectiveness of unilateral vs. bilateral stimulation of both targets. Results suggest that high-frequency stimulation of either the EPN or STN significantly decreases the incidence of oral dyskinesias induced by chronic haloperidol.

2. Materials and methods

All procedures were approved by the Animal Care Committee at the Centre for Addiction and Mental Health and complied with Canadian Council on Animal Care (CCAC) and NIH standards and guidelines.

2.1. Drug treatment

Male Sprague–Dawley rats initially weighing 200–250 g (Charles River, Quebec) received either haloperidol decanoate (HAL; 21 mg/kg i.m. N=68) or sesame oil vehicle (N=22) once every 3 weeks for 12 weeks (a total of four injections). The decanoate formulation is known to result in constant plasma levels in the 1.1–1.5 mg/kg range and reliably induce progressively increasing levels of VCMs (Turrone et al., 2002). VCM assessments were conducted once a week in a quiet room, beginning 1 week before the first HAL injection. For each VCM assessment the rat was placed on a flat round surface (26 cm in diameter, 50 cm high) and allowed to acclimate for 2 min. Over the following 2 min a trained observer recorded the number of VCMs, which were defined as jaw movements in the vertical plane not directed at specific objects accompanied or not by tongue protrusions. Discrete bursts of jaw tremors were counted as one VCM.

2.2. Surgery

After 12 weeks of HAL treatment, rats were anesthetized with ketamine/xylazine (100/7.5 mg/kg i.p.) and had polymide-insulated stainless steel monopolar electrodes (250 μm in diameter with 0.6 mm of surface exposed) bilaterally implanted into the STN (AP −3.8 mm; ML +3.5 mm; DV −8.0) or EPN (AP −3.6 mm; ML +3.6 mm; DV −7.8 mm) (Paxinos and Watson, 1986). Anodes were connected to a bone screw over the somatosensory cortex. Sham surgery controls were anesthetized and had holes drilled into the skull but were not implanted with electrodes. A second group of control animals had electrodes implanted into either the STN or EPN, but no current was passed through the electrodes at any time.

2.3. DBS protocol

Starting 1 week after surgery DBS was applied using a handheld stimulator (St Jude Medical Model 6510, Plano, Texas) set to deliver a 100 μA current at 90 μs pulse width. Choice of stimulation settings was guided by two considerations. First, when electrode diameter and exposed surface are taken into account, we estimated that current intensities in the 100–300 μA range would approximate those used in humans. Second, preliminary observations indicated that currents higher than 100 μA induced motor effects in some animals (i.e. forelimb dyskinesias in the STN group and motor contractions in the EPN group). During the DBS sessions, rats were initially given a 2-min acclimation period on the observation pedestal followed by a 2-min baseline VCM assessment. Thereafter, stimulation was delivered for 2 min at each of the following

conditions: (a) bilateral 130 Hz; (b) bilateral 60 Hz; (c) bilateral 30 Hz; (d) left unilateral 130 Hz; and (e) right unilateral 130 Hz. The order of these 5 stimulation conditions was randomized for each subject, with at least 20 s between them. After stimulation was turned off, an additional 2-min observation was conducted to assess recovery of the behaviour. Tests were conducted on two days with each animal receiving 2 trials at each of the 5 stimulation conditions. Bilateral and unilateral data were analyzed separately using two-factor ANOVAs with repeated measures on the factor Frequency, followed where appropriate by paired or unpaired t tests for two group comparisons.

2.4. Open field tests

After completion of VCM assessments, locomotor activity was assessed in an open field. Rats were placed in automated activity chambers (Med Associates, St. Albans, VT) for a 2-min acclimation period before the onset of DBS (for animals implanted with electrodes). Horizontal activity was then recorded for 10 min during 130 Hz DBS, following which rats were returned to the home cage. Animals without electrodes were also monitored in the activity chamber for 12 min.

2.5. Verification of electrode placements

Following behavioural tests, rats were deeply anesthetized with sodium pentobarbital and brains were removed, sectioned, post-fixed in 10% formalin vapour and stained with cresyl violet.

3. Results

As expected, VCMs developed after initiation of HAL treatment and continued to rise in frequency until approximately 7–8 weeks of treatment in most animals. VCM counts for the 3 weeks immediately prior to surgery were averaged and served as a pre-surgery VCM baseline measure. When the first post-surgery VCM assessments were compared to the pre-surgery baseline no significant differences were observed (Figs. 2 and 3), indicating that surgery per se had no effect on VCMs counts.

3.1. Electrode localization

Fig. 1 shows all electrode placements, both inside (filled circles) and outside (open circles) the two target areas for rats that completed the study (i.e. excluding attrition due to loss of electrode caps). Only rats with both left and right electrodes within the target areas (filled circles in Fig. 1) were considered in the final analyses. It was not possible to find a consistent pattern of DBS effects for rats with electrode placements outside the two target areas (open circles in Fig. 1). DBS in HAL-treated rats with electrodes outside the EPN or STN but within the internal capsule or the substantia nigra pars reticulata appeared to reduce VCMs. However, given the proximity of these electrodes to the EPN and STN, respectively, it was not possible to rule out the possibility that such effects were due to current spread to the intended targets.

3.2. Effects of bilateral STN stimulation

As shown in Fig. 2, HAL-treated animals that received bilateral STN DBS at 30 Hz, 60 Hz or 130 Hz showed significant reductions in VCM counts (Frequency main effect $F=17.79$ $p<0.001$; Frequency × Drug, $F=16.98$ $p<0.001$). Stimulation at each of the tested frequencies resulted in significant decreases in VCMs compared to the no-stimulation post-surgery baseline (30 Hz: −40.2%, $p<0.01$; 60 Hz: −46.4%, $p<0.0001$; 130 Hz: −61.7% $p<0.001$) (Fig. 2). In addition, mean VCM scores for the 130 Hz condition were significantly lower than those for the 30 Hz condition ($p<0.001$) (Fig. 2).

3.3. Effects of bilateral EPN stimulation

Similarly to what was observed in the STN group, bilateral EPN DBS significantly reduced VCMs at all frequencies tested when compared to the no-stimulation baseline (30 Hz: −48.9%, $p<0.001$; 60 Hz: −49.0%, $p<0.001$; 130 Hz: −50.8%, $p=<0.001$) (Fig. 3). No significant differences were observed among the three stimulation frequencies (Fig. 3).

3.4. Effects of unilateral stimulation

Unilateral stimulation of either the right or the left STN was associated with significantly fewer VCMs relative to baseline (right = −38.5%, $p=0.021$; left = −35.5%, $p=0.014$) (Fig. 2). A similar pattern was observed in the EPN (Fig. 3): unilateral stimulation of either the right or the left EPN significantly reduced VCM counts relative to baseline (right = −48.1%, $p=0.011$; left = −36.5%, $p=0.045$). In both STN and EPN, 130 Hz bilateral stimulation appeared to be more effective than 130 Hz unilateral stimulation (Figs. 2 and 3). However the differences were not statistically significant in either case.

3.5. DBS effects in vehicle controls

As shown in Figs. 2 and 3, DBS applied bilaterally or unilaterally to either the STN or EPN induced no significant VCMs in vehicle-treated controls, irrespective of frequency used.

3.6. Surgery controls

Animals that underwent sham surgery exhibited similar levels of VCMs in the three assessments prior to surgery (HAL mean = 10.78 ± 1.75, N = 6; VEH mean = 1.25 ± 0.37; N = 4) as they did after surgery (HAL mean = 11.36 ± 1.45; VEH mean = 1.37 ± 0.38). Likewise, HAL-treated animals that were implanted with electrodes but that never received DBS showed similar levels of VCMs prior to (mean STN = 11.83 ± 0.17 N = 2; mean EPN = 9.17 ± 0.17 N = 2) and after surgery (mean STN = 9.00 ± 1.68; mean EPN = 9.50 ± 1.32).

3.7. Effect of stimulation on open field activity

As expected, HAL-treated animals showed less ambulatory activity in the open field than vehicle-treated animals at all time points (Fig. 4A). A 3-way ANOVA with repeated measures on the factor Time revealed a main effect of Drug treatment ($F=12.85$, $p<0.001$), a significant main effect of Time ($F=2.74$, $p=0.02$), but no significant main effect of DBS Target and no Time × Target interaction (both $ps>0.05$). Among HAL-treated rats, those receiving STN DBS exhibited similar levels of locomotor activity as HAL sham-operated animals at all time points (Fig. 4A). In contrast, HAL-treated animals receiving EPN DBS had higher activity levels than the other HAL-treated

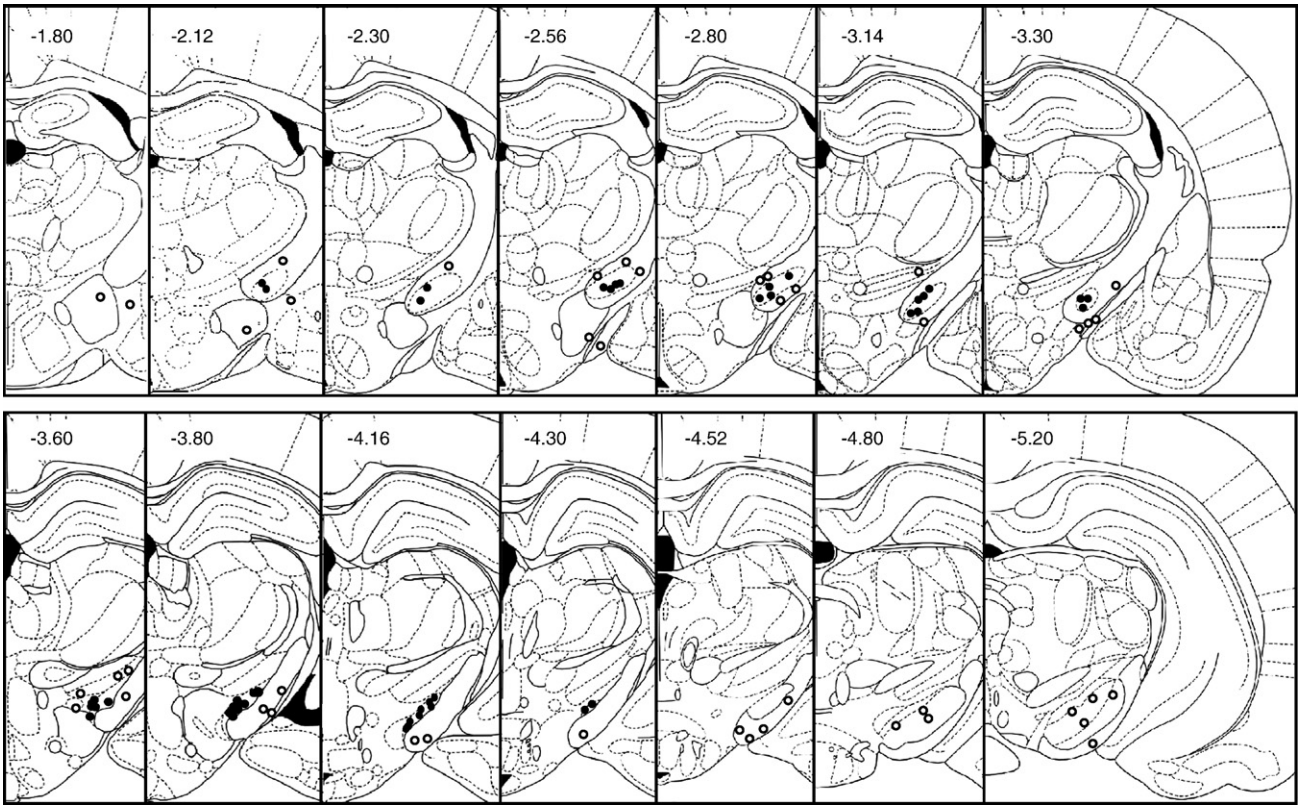

Figure 1 Electrode localization. Electrode placements for all animals that completed the study. Filled circles indicate placements within the STN and EPN, open circles placements outside these two target areas. Note that only animals with both electrodes placed within the STN or EPN were included in the final data analyses. The number at the top of each panel corresponds to distance from bregma in mm, according to the Paxinos and Watson 1998 atlas (reproduced with permission).

groups ($p<0.05$ in both cases) and did not differ from their VEH-treated counterparts. In vehicle-treated groups, there were no differences between rats receiving DBS at either anatomic target or sham-operated animals at any time point (Fig. 4A).

When total cumulated activity scores were considered (Fig. 4B) similar results were obtained following a 2×2 factorial ANOVA. The total activity score of HAL-treated animals was lower than that of their VEH-treated counterparts in all cases

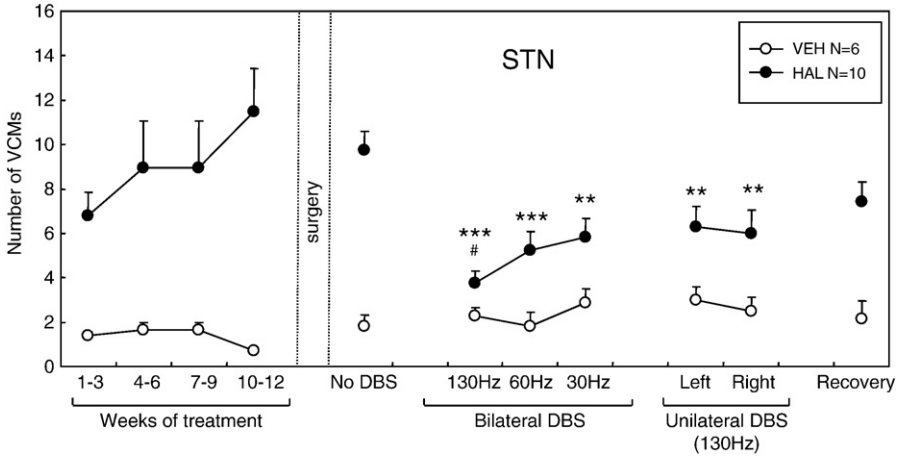

Figure 2 Effects of STN DBS on VCMs. Values are means ± sem. The order of the 5 stimulation conditions (bilateral 30, 60 and 130 Hz; unilateral right, unilateral left 130 Hz) was randomized for each rat. Note that due to randomization of conditions, the recovery period followed different stimulation conditions. Bilateral STN DBS at all frequencies tested significantly reduced VCMs relative to baseline. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, paired t tests. Bilateral 130 Hz DBS reduced VCMs to a greater extent than 30 Hz stimulation (# $p=0.003$, independent t test).

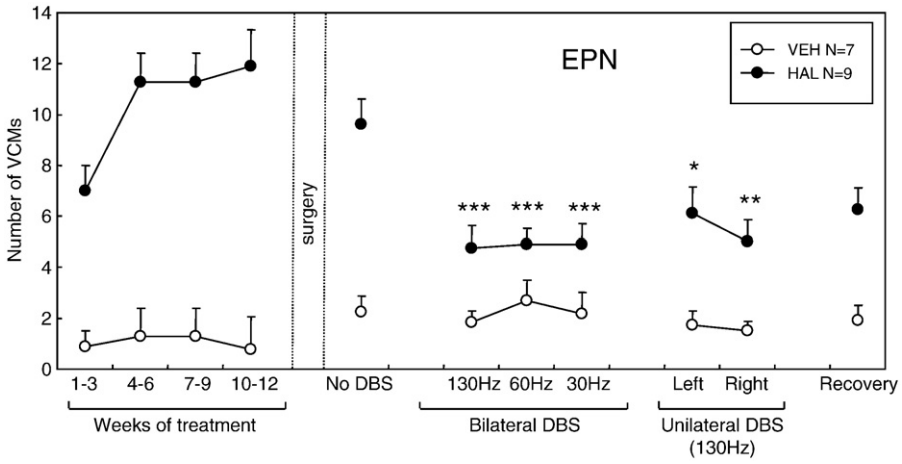

Figure 3 Effects of EPN DBS on VCMs. Values are means ± sem. The order of 5 stimulation conditions (bilateral 30, 60 and 130 Hz; unilateral right, unilateral left 130 Hz) was randomized for each subject. Because of randomization the recovery period did not always follow the same stimulation condition. Bilateral DBS of the EPN significantly reduced VCMs in HAL-treated animals at all frequencies tested relative to baseline (*** $p<0.001$, paired t tests). There were no significant differences between stimulation frequencies for either HAL- or VEH-treated rats. Unilateral EPN stimulation significantly reduced VCM counts relative to baseline (* $p<0.05$, ** $p<0.01$, paired t tests).

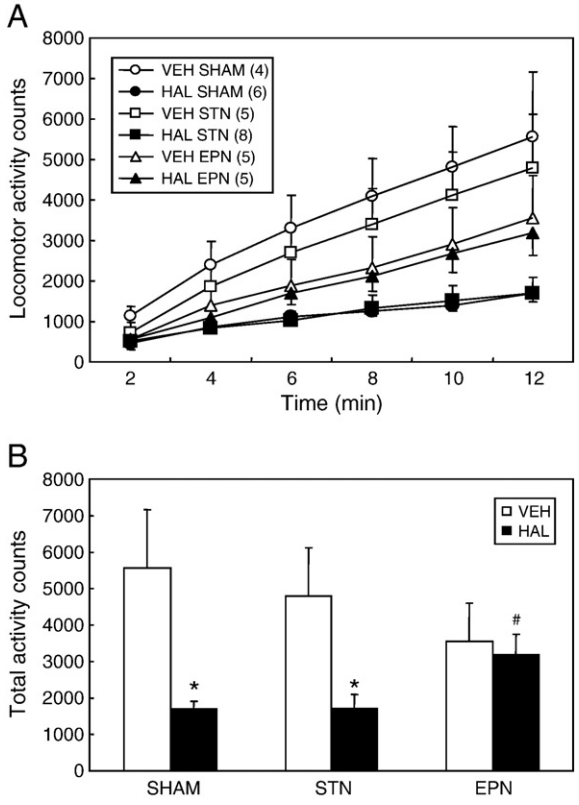

Figure 4 DBS effects on open field activity. In both panels, values are means ± sem. Animals were run in an activity chamber once with a 2-min acclimation period followed by 10 min of 130 Hz DBS. Group Ns are shown in parentheses. A: Cumulative activity over 12 min. HAL-treated groups were generally less active than VEH-treated groups across time intervals, but there was no significant main effect of Target and no Target × Treatment interaction. B: Total activity summary for data in panel A. * $p<0.05$, HAL-treated vs. corresponding VEH-treated group. # $p<0.05$, compared to either HAL-SHAM or HAL-STN groups.

($p<0.05$, independent t tests), except for HAL-treated rats receiving EPN DBS; this group did not differ from its stimulated VEH-EPN counterpart ($p>0.05$) and showed significantly higher activity than either HAL-SHAM or HAL-STN rats ($p<0.05$ in both cases)(Fig. 4B).

4. Discussion

The main finding of this study was that DBS applied to either the EPN or the STN effectively reduced the number of VCMs in HAL-treated rats. In addition, unilateral stimulation of these nuclei was also effective in reducing oral dyskinesias. These effects were not due to an overall effect of DBS on motor activity levels, as shown by open field results. In vehicle-treated controls DBS at the settings used did not induce dyskinetic orofacial movements, whether applied bilaterally or unilaterally to either anatomical target. To our knowledge, this is the first examination of DBS effects in the chronic HAL VCM model of TD.

We observed pronounced effects of DBS on VCM counts using standard 2-min observation periods, as used in a vast number of previous studies assessing the efficacy of pharmacological agents in the HAL-induced VCM model of TD (Egan et al., 1996b; Turrone et al., 2002). In our experience longer observation periods do not increase the reliability of VCM assessments. Under these conditions, we found that 2 min of DBS led to significant decreases in VCMs. In most dystonic syndromes, the rate and timeframe for improvement is quite variable, with some patients showing immediate improvement and others taking longer. In general however improvement builds up with time. Phasic dystonic movements tend to improve rapidly after stimulation onset while tonic movements improve at a slower rate. In the present study we were specifically interested in the acute effects of DBS, in part because in the clinic motor abnormalities are often seen to decrease nearly immediately after DBS onset (McIntyre et al., 2004). In the specific case of

TD, immediate alleviation of motor symptoms has been reported (Schrader et al., 2004). Future studies will address the effects of prolonged and chronic stimulation. In pilot work we have observed VCM decreases for up to 4 h of DBS delivered to the STN or EPN without any observable adverse effects (data not shown).

In the present study VCM levels were similar before surgery and in the first postoperative assessments prior to DBS in animals implanted with EPN or STN electrodes, thus ruling out the possibility that surgery or mere insertion of electrodes could have played a role in the observed results. Neither, as noted, were the observed effects of DBS on VCMs due to nonspecific depressing effects of DBS on motor activity. Indeed, the open field data indicated that in the EPN group DBS seemed to actually counter the general hypoactivity induced by HAL.

The main intent of the present study was to provide an initial assessment of the viability of the HAL VCM model to investigate DBS effects, and thus our study did not address mechanistic possibilities for the observed effects. As in patients with dystonia, the neural elements involved in DBS-mediated reduction in VCMs are still unclear. Commonly accepted mechanisms of DBS at high frequency include a functional inactivation of local neuronal populations and the modulation of structures at a distance from target (e.g. through the activation of fiber pathways nearby the electrodes) (Lozano et al., 2002b; Vitek, 2002). This is supported by a recent study demonstrating that driving afferent axons to the STN with high-frequency stimulation attenuates motor symptoms in unilateral 6-OHDA lesioned rats (Gradinaru et al., 2009). Among possible mechanistic processes to be investigated in future work is the possibility that stimulation induces a "functional lesion effect" or modulates pathological network activity induced by chronic haloperidol treatment (Lozano et al., 2002a; McIntyre et al., 2004). As a potent dopamine D2 antagonist, haloperidol reduces the inhibitory effect of DA in the so-called indirect basal ganglia output pathway (Albin et al., 1989), resulting in disinhibition of the STN, increased activity of the EPN (GPi) and, as a consequence, over-inhibition of the motor thalamus. Thus, DBS applied to either the STN or EPN (GPi) may conceivably correct pathological network activity by decreasing output from these two structures. In line with this possibility, STN lesions have been reported to alleviate VCM in rats (Stoessl and Rajakumar, 1996).

While DBS of the GPi has been the mainstay of surgical treatments for TD (Damier et al., 2007; Eltahawy et al., 2004; Kefalopoulou et al., 2009; Kosel et al., 2007; Sako et al., 2008; Schrader et al., 2004), it has been argued that the STN DBS may be at least as effective (Sun et al., 2007). Controlled clinical trials have not yet been conducted to support the superiority of either target in TD. Here we have compared DBS of the STN and EPN in a model system, and our results fail to demonstrate significant functional differences between these two neuroanatomical targets. Of interest however, our results suggest that frequency of stimulation did play a different role in the effects of stimulation at each target. In the STN, DBS at 130 Hz was significantly more effective than at 30 Hz, whereas no differences across frequencies were apparent in animals receiving EPN stimulation. Although similar effects have not been clearly demonstrated in patients with TD, the present findings are largely consistent with the DBS literature in dystonia and Parkinson's disease. In both conditions, frequencies above 100 Hz appear to be optimal for alleviation of motor symptoms after STN stimulation (Kleiner-Fisman et al., 2006; Moro et al., 2002). In contrast, the ideal frequency for pallidal stimulation in patients with dystonia is still controversial. While most centers use frequencies in the 130 Hz range, others have recently suggested that 60 Hz would be equally effective (Alterman et al., 2007).

Another consideration is the possibility that brain tissue may adapt to stimulation frequency over time (Volkmann, 2004). Our results suggest that with EPN, but not STN stimulation, the frequency of stimulation can be varied in order to avoid habituation and this would not sacrifice efficacy. Although caution must always be exerted in extrapolating data from animal models to humans, our results suggest that pallidal DBS at lower frequencies would be effective in TD. This however still needs to be demonstrated in clinical trials.

Also of interest was the clear effectiveness of unilateral DBS when applied to either anatomical target. This is consistent with clinical reports in TD patients (Schrader et al., 2004). Yet, in the case of the STN, but the EPN, our results seem to suggest a stronger effect of bilateral vs. unilateral DBS on VCMs.

Because of its dramatic results, clinical application of DBS has advanced much more quickly than preclinical knowledge (McIntyre et al., 2004). In order to optimize the applications of DBS for TD, preclinical investigations will be needed to help elucidate the mechanisms underlying the effects of DBS in this disorder. Here we show that DBS applied bilaterally or unilaterally to either the EPN or the STN significantly reduced VCMs in rats undergoing long-term HAL treatment. The present model has permitted us to behaviorally characterize the effects of DBS at different frequencies and anatomical targets, and may thus provide a very useful preparation for the study of neuronal mechanisms underlying these effects.

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Contributors

MC and JNN designed the experiments and wrote the manuscript. MC conducted all of the experimental work and analyses. CH gave expert opinion, contributed to the writing and reviewed the manuscript.

Conflict of interest

CH is a consultant for St Jude Medical.

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