Published in final edited form as:

Neuroimage. 2015 January 15; 105: 181–188. doi:10.1016/j.neuroimage.2014.09.064.

Frequency-dependent functional neuromodulatory effects on the motor network by ventral lateral thalamic deep brain stimulation in swine

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Abstract

Thalamic deep brain stimulation (DBS) is an FDA-approved neurosurgical treatment for medication-refractory essential tremor. Its therapeutic benefit is highly dependent upon stimulation frequency and voltage parameters. We investigated these stimulation parameter-dependent effects on neural network activation by performing functional magnetic resonance imaging (fMRI) during DBS of the ventral lateral (VL) thalamus and comparing the blood oxygenation level-dependent (BOLD) signals induced by multiple stimulation parameter combinations in a within-subjects study of swine. Low (10 Hz) and high (130 Hz) frequency stimulation was applied at 3, 5, and 7 volts in the VL thalamus of normal swine ($n = 5$). We found that stimulation frequency and voltage combinations differentially modulated brain network activity in the sensorimotor cortex, the basal ganglia, and the cerebellum in a parameter-dependent manner. Notably, in the motor cortex, high frequency stimulation generated a negative BOLD response, while low frequency stimulation increased the positive BOLD response. These frequency-dependent differential effects suggest that the VL thalamus is an exemplary target for investigating functional network connectivity associated with therapeutic DBS.

Keywords

Ventral lateral thalamus (VL Thalamus); Deep brain stimulation (DBS); Essential tremor (ET); Low frequency stimulation (LFS); High frequency stimulation (HFS); and fMRI

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The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

Introduction

Thalamic deep brain stimulation (DBS) is a well-established restorative therapy for movement disorders, such as tremor-dominant Parkinson's disease (PD) (Benabid, 2003) and essential tremor (ET) (Benabid et al., 1993). Although the mechanisms of DBS are not fully understood, studies performed in clinical and research settings support the use of DBS over surgical ablation for two main reasons: DBS is reversible, and stimulation parameter adjustments provide more individualized treatment (Ushe et al., 2004; Adey et al., 1959; Benabid et al., 1987; Humphries et al., 1982; Pahwa et al., 2001; Tasker et al., 1982). Stimulation parameter adjustments are critical in optimizing DBS clinical outcomes.

In previous studies, thalamic DBS effectively suppressed tremor at frequencies ranging from 150 to 1000 Hz with the lowest current applied (Benabid et al., 1991); however, at low frequencies, higher voltage was required to produce the same effects (Benabid et al., 1991; Kuncel and Grill, 2004; Limousin et al., 1995). Frequencies ranging from 60 to 1000 Hz have been effective for symptom relief. To balance battery power consumption against therapeutic benefit, the clinical frequency of choice is usually 130 Hz (Kuncel and Grill, 2004; Volkmann et al., 2002). It has been widely reported that high frequency (HFS) thalamic DBS of >130 Hz is very effective in tremor suppression, while low frequency stimulation (LFS) of < 60 Hz aggravates tremor (Bejjani et al., 2000; Constantoyannis et al., 2004). Computational modeling based on cellular response to extracellular thalamic stimulation demonstrates that HFS reduces the output firing rate of thalamocortical neurons by masking the intrinsic burst activity, while LFS increases the output firing rate by supplementing the amplitude of intrinsic burst activity (Kuncel et al., 2007). However, the effect of variations in stimulation parameters on neural network activity has been difficult to elucidate.

Functional imaging studies have been used to characterize the stimulation parameter-dependent neural circuit changes in an effort to understand thalamic DBS mechanisms in humans with ET and Parkinsonian tremor (Ceballos-Baumann et al., 2001; Haslinger et al., 2003; Parker et al., 1992). These studies suggest that the cerebellothalamo-cortical pathway plays a crucial role in tremor suppression. However the reported brain activation sites and patterns of activity are inconsistent across such studies.

In this study, we investigated the differences in neural circuitry activation between HFS and LFS of the ventral lateral (VL) thalamus by combining DBS and functional magnetic resonance imaging (fMRI) in a large animal (swine) within-subjects design. The combination of DBS and fMRI provides a powerful means for testing the modulatory effects of electrical stimulation on neuronal network activity *in vivo* (Kim et al., 2013; Min et al., 2012). VL thalamus is an element of the well-defined cerebellothalamo-cortical pathway, which is less complex than other DBS targets such as the subthalamic nucleus (STN) or the globus pallidus interna (GPI). It thus provides an ideal model for *in vivo* studies of functional connectivity (Morel et al., 2005; Rouiller et al., 1994; Sakai et al., 1996).

Our results show that VL thalamic DBS alters the activity and dynamics of the cerebello-thalamo-cortical network in a stimulation parameter-dependent manner. These findings

provide important insights into the frequency-dependent functional neuromodulatory effect of thalamic DBS.

Materials and Methods

Subjects and DBS electrode implantation

All study procedures were performed in accordance with the National Institutes of Health Guidelines for Animal Research (Guide for the Care and Use of Laboratory Animals) and approved by Mayo Clinic Institutional Animal Care and Use Committee. The subject groups consisted of five normal ($n=5$), domestic male swine weighing 35 ± 5 kg. Animals were housed individually in a controlled environment with humidity at 45%, temperature at 21°C , with once daily feeding and access to water ad libitum. Each subject was initially sedated with Telazol (5 mg/kg i.m.) and Xylazine (2 mg/kg i.m.) and maintained with 1.5 – 3 % isoflurane during surgery and 1.5 – 2 % isoflurane during the fMRI experiments. The vital signs (heart rate: ~ 120 bpm, and temperature: $36\text{--}37^{\circ}\text{C}$) were monitored continuously and respirations were maintained at 12 breaths per minute throughout the procedures. An MRI-guided Leksell stereotactic targeting system (Elekta, Stockholm, Sweden) with a MRI-compatible stereotactic head frame designed specifically for large animal use (Mayo Clinic, Rochester, Minnesota) was used for DBS electrode targeting and implantation (Min et al., 2012). Imaging was conducted by a 3.0-T MR scanner (Signa HDx, General Electric, Fairfield, Connecticut) with an in-house designed 4-channel phased array radiofrequency (RF) coil (Mayo Clinic, Rochester Minnesota) (Min et al., 2012). COMPASS navigational software, modified to accommodate the swine head frame coordinates, was used to perform MR image-based targeting with the pig brain atlas as a reference (Felix et al., 1999). Stereotactic coordinates for the DBS electrode implantation trajectory were determined for the right unilateral VL thalamus.

A quadripolar DBS electrode (Model 3389, Medtronic, Minneapolis, Minnesota) was implanted. The most distal contact was labeled “0” and the most proximal as “3”. The mean $\pm$ standard deviation coordinates for contact 0 were: $x = 5.03 \pm 0.05$ mm lateral to the intercommisural (AC-PC) line; $y = 1.47 \pm 0.24$ mm anterior from the AC; $z = 1.29 \pm 1.64$ mm inferior from the AC-PC (Supplementary Fig. 1).

fMRI and DBS

Following the DBS surgery, six fMRI experiments were conducted using LFS (10Hz) and HFS (130Hz) with three different amplitude intensities (3V, 5V and 7V). Biphasic stimulation was applied through 0 (–) and 1 (+) contacts of the DBS lead with a pulse width of 90 μs . There was a 10 min rest interval between conditions. The DBS lead was connected via extension wiring to a Mayo Investigational Neuromodulation Control System (MINCS), an in-house developed wireless stimulation system that was located outside of the scan room (Chang et al., 2013). The DBS electrode impedance was examined immediately after implantation and was continuously monitored during MRI scanning to validate lead integrity and evaluate charge density.

Gradient echo echo-planar imaging pulse sequence was used for the fMRI scan (parameters: repetition time/echo time = 3000/34.7 ms; flip angle = 90°; coronal cut; field of view 15 × 15 cm; matrix = 64 × 64; slice thickness = 2.4 mm; slice number = 32; frequency encoding direction = right-left; spectral pulse for fat suppression). To eliminate physical motion during the fMRI experiment, the animals were administered a muscle relaxant, either pancuronium bromide or vecuronium bromide (2 mg bolus and maintained with 3 mg/hr, i.v.). To minimize geometric distortion, we set the EPI bandwidth parameter to 62.5 and set the frequency encoding direction to Right-Left (Min et al., 2012). However, the susceptibility artifact could not be removed due to electrode composition (Platinum-Iridium), resulting in a signal (below 2000 signal intensity) and volume (~2.4 mm in diameter, or 1 voxel, and ~7.0 mm in diameter, or 3 voxels) loss in brain regions immediately surrounding the electrode connection wires and lead, respectively (Supplementary Fig. 2). Therefore, we adjusted the trajectory of the DBS electrode during surgical targeting in order to minimize imaging artifact in our regions of interest, such as the motor cortex, major areas of the basal ganglia, and cerebellum.

A block design was used to detect putative BOLD signal responses evoked by electrical stimulation, acquiring five stimuli (6 sec) with 60 sec intervals (Min et al., 2012; Knight et al., 2013). The six conditions were tested in a fixed order, having 10Hz (3V, 5V, 7V) first, followed by 130Hz (3V, 5V, 7V). A 10-min rest interval was given between stimulations, thereby allowing recovery from stimulation. However, we cannot rule out the possibility that latent neurologic interactions from previous stimuli may have subtle influences on later imaging paradigms.

Data processing and analysis

The acquired fMRI data was subjected to standard pre-processing steps, including temporal filtering, slice scan time correction, three-dimensional motion correction and spatial smoothing (Gaussian filter with full width at half maximum: 1.1 pixel size in 2D frequency domain) implemented in Brain Voyager QX software (Maastricht, Netherlands). A modified double-gamma hemodynamic response function was used to cover both positive and negative BOLD signal changes to correlate with the given stimulus protocol (onset = -6 s, time to response peak = 15 s, time to undershoot peak = 25 sec). The fMRI dataset was normalized to the 3D pig brain MRI atlas (Saikali et al., 2010) using a nonlinear co-registration based on the anterior and posterior commissure points and six boundaries of the brain (anterior, posterior, superior, inferior, right and left borders) using each subject's 3D MP-RAGE image (Brain Innovation, BrainVoyager QX) (Min et al., 2014). These datasets were further analyzed using linear regression analysis with the general linear model and multi-subject analysis. To correct for multiple comparisons and exclude false positive voxels, we considered only voxels with a False Discovery Rate (FDR) significance level of < 0.001 as representing sites of activation (Table 1). In addition to and separate from the FDR, we applied the more stringent Bonferroni correction (<0.001) to the original data. The brain areas that survived Bonferroni correction are marked in Table 1. To measure event-related BOLD response, regions of interest (ROI) based on the atlas were selected from clusters of functional activation identified by the normalized averaged group data for each brain area. This BOLD signal intensity change (%), representing minimum or maximum

response intensities within each cluster, was labeled “BOLD % change” (mean $\pm$ SEM). The total voxel size of the ROI was measured (mm^3), and compared as cluster size difference in % change (Min et al., 2012; Kim et al., 2012).

After the fMRI study, animals were euthanized (pentobarbital, 100 mg/kg i.v.) in accordance with institutional animal care guidelines. The brain was then collected and stored in paraformaldehyde (4%). Then, using a frozen microtome (SM2010 R, Leica Biosystems, Nussloch, Germany), the brain was sectioned in 250–700 μm thick slices in coronal, or sagittal orientations to confirm electrode lead locations (Supplementary Fig. 1B).

Results

To determine the effect of stimulation frequency on neural network activation, 10 Hz and 130 Hz (5 V with 90 μs pulse width) stimulations were applied to the VL thalamus of 5 adult swine in a within-subjects design. The brain areas induced by VL DBS are listed in Table 1 with additional information on cluster size, location, and possible circuits involved based on available anatomical literature.

Stimulation Frequency Effects

We found that LFS increased BOLD signal predominantly in the sensorimotor network, including the ipsilateral primary motor cortex (PRIMC), premotor cortex (PREMC), and primary somatosensory cortex (PSS) ($\text{FDR} < 0.001$). Areas of activation also included the ipsilateral prefrontal cortex (PFC) (Table 1, Fig. 1A). LFS did not yield any significant BOLD activation in subcortical areas (Table 1).

HFS also affected the sensorimotor network, but it significantly decreased rather than increased BOLD responses in the ipsilateral PRIMC and PREMC ($\text{FDR} < 0.001$) (Fig. 1C). HFS did increase BOLD signal in the ipsilateral PSS, the somatosensory association cortex (SAC), and the contralateral cerebellum. Other areas that showed activation by HFS ($\text{FDR} < 0.001$) include: 1) the associative circuit, including PFC; 2) the limbic circuit, including the dorsal anterior, dorsal posterior cingulate cortices, the insular cortex, perirhinal cortex, and parahippocampal gyrus; and 3) the basal ganglia circuit, including the caudate, putamen, and substantia nigra (Table 1).

The event-related time course of BOLD % change for each ROI was plotted as % change in BOLD signal vs. time (one scan is equal to 3 sec). As seen in Fig. 1B, there was a signal decrease (negative BOLD response) as measured by BOLD % change during HFS and an increase after stimulation was terminated in the PRIMC and PREMC. With LFS the PRIMC and PREMC showed positive BOLD % change which represents the general delayed hemodynamics peaking at 12 s.

Amplitude effects

To address the effect of current spread in these frequencies, we assessed the voltage amplitude effect in both LFS and HFS as seen in Fig. 2. Notably, the DBS-induced BOLD activation of brain areas overlapped within each frequency as amplitude increased (Fig. 2A and B). In Fig. 3, we compared the time course of fMRI BOLD signal change and cluster

size. Three different amplitudes (3, 5, and 7 V) were applied, and six representative associative and sensorimotor network regions were selected for this comparison: PFC, PRIMC, PREMC, PSS, SAC, and cerebellum.

In the PRIMC and PREMC both LSF and HSF resulted in a steady increase in cluster size of $15.9 \pm 2.8\%$ as the amplitude (V) increased. LFS resulted in a significantly greater BOLD % change as amplitude increased from 3V to 5 V and 7 V in PRIMC and PREMC (Fig. 3A, $p < 0.001$, t-test). In the PRIMC cluster size increased 22% and 39% for 5 V and 7 V, respectively when compared to 3 V. In the PREMC cluster size increased 13 % and 36 %, at 5 V and 7 V, respectively when compared to 3 V (Fig. 3B).

With HFS the negative BOLD peak showed a significant increase as the stimulation amplitude increased, although the latent positive BOLD peak showed no difference in the PRIMC and PREMC. Both PRIMC and PREMC showed negative BOLD peak differences when comparing 3 V to 7 V ($p < 0.001$, student t-test). There was a significant difference between 5 V and 7 V ($p < 0.05$) in PRIMC, and between 3 V and 5 V in PREMC ($p < 0.05$) (Fig. 3A). Similarly, PRIMC showed a cluster size increase of 33% when amplitude increased from 3 V to 7 V and an increase of 29% when amplitude increased from 5 V to 7 V. However there was only a 4% increase in cluster size when amplitude increased from 3 V to 5 V. The PREMC showed cluster size increase between 3 V and 7 V of 19%, 3 V and 5 V of 9%, and between 5V and 7V of 10%. PFC (HFS), PSS (HFS) and SAC (HFS) showed increases in cluster size from 3 V to 5 V ($11.3 \pm 2.9\%$) and showed decreases in cluster size from 5 V to 7 V ($9.5 \pm 3.9\%$) (Fig. 3B).

In conclusion, for LFS, the cluster size increased with increasing voltage in the PFC, PRIMC, PREMC, and PSS. With HFS, the cluster size increased with increasing voltage in the PRIMC, PREMC, and CB; however, in the PFC, PSS, and SAC, the volume of activated area increased from 3 V to 5 V, and decreased at 7 V.

Discussion

The frequency-dependent therapeutic effect of thalamic DBS was already known in the 1950s and 60s, where prior to conducting thalamotomy to treat tremor, enhancement of tremor with LFS (5–10 Hz) and/or attenuation with HFS (50–100Hz) was taken as a favorable sign for target accuracy (Blomstedt and Hariz, 2010; DeLong and Wichmann, 2012). In thalamic DBS, LFS aggravates tremor (Bejjani et al., 2000; Kuncel et al., 2007) and even creates myoclonus tremor in non-tremor patients suggesting a central oscillatory mechanism involving the olivocerebellar complex and the thalamus (Constantoyannis et al., 2004). Other DBS targets such as STN have been reported to have LFS-dependent symptom aggravation but the aggravation is generally minimal (Kuncel et al., 2007; Lai et al., 2014; Moro et al., 2002).

In our study, VL thalamic DBS differentially modulated global neural activity in accordance with stimulation frequency and voltage. VL thalamic DBS produced a significant BOLD effect in the sensorimotor cortex, the subcortical basal ganglia circuitry, and the cerebellum. In addition, our results showed differential functional activity between HFS and LFS in the

motor cortex, where HFS generated a negative BOLD response while LFS generated a positive BOLD response in the same area. Increasing the stimulation amplitude (voltage) of DBS increased both BOLD % change and the size of the affected brain area (cluster size), suggesting that larger electrical spread recruits more cell bodies and/or axonal fibers (McIntyre and Hahn, 2010). Additionally, our data suggest that VL thalamic DBS might spread via both orthodromic and antidromic connections (see Table 1 for possible circuits involved).

Our results are also consistent with current understanding of the anatomical projections of the VL thalamus. Anatomic studies indicate that the VL thalamic area can be divided into two major functional circuits in the cerebello-thalamo-cortical network; one is an anterior basal ganglia-thalamocortical motor loop, and the other is a posterior cerebello-thalamocortical loop (Asanuma et al., 1983; Ilinsky and Kultas-Ilinsky, 2002; Kultas-Ilinsky and Ilinsky, 1991). Previous PET imaging studies suggest cortical activation in the cerebello-thalamocortical pathway may play a crucial role in tremor suppression (Ceballos-Baumann et al., 2001; Haslinger et al., 2003). Regional cerebellar blood flow (rCBF) PET studies in thalamic DBS for ET demonstrated that high frequency DBS (130 Hz) increased rCBF in the ipsilateral cortex compared with nontherapeutic low frequency DBS (50 Hz) (Ceballos-Baumann et al., 2001; Haslinger et al., 2003). However, in an earlier study, initial decrease of rCBF at the ipsilateral somatosensory cortex, supplementary motor cortex, caudate, vermis and contralateral cerebellum with HFS thalamic DBS was reported (Parker et al., 1992). Although our results support the later, the inconsistency may be due to imaging modality or disease state baseline differences. There is also a temporal resolution difference between fMRI and PET. In the previous PET studies, each measurement was taken for either 60 second-(Ceballos-Baumann et al., 2001) or 15 minute-stimulation periods (Perlmutter et al., 2002). In the present fMRI experiment, a six second-duration stimulation induced an initial negative BOLD response followed by a positive response, suggesting the possibility of a biphasic neuronal response (Destexhe et al., 1996). Another possible reason for this response may be that thalamic DBS initially activates cortical GABAergic neurons, which inhibit regional cortical neurons, but could have variant hemodynamic responses (Logothetis, 2008).

In 2006, Iremonger et al. published that thalamic HFS prolonged the suppression of activity with the motor cortex (M1) (Iremonger et al., 2006). In this paper, they showed multiple initial responses to HFS, which depend on the status of cortical neuronal excitability. At resting membrane potential, HFS evoked excitatory postsynaptic potential (EPSP) in M1; however, at the excitable level where spontaneous action potentials are generated, responses to HFS were varied including short hyperpolarization and reduction or cessation of firing at the onset of stimulation. The authors also used picrotoxin and CGP-55845 at the resting membrane potential and increased the HFS-evoked synaptic response, thereby concluding that GABAergic inhibitory synaptic currents may play a crucial role HFS-evoked responses. Subsequent investigations found that frequency-dependent responses are due to astrocytic activation within the thalamus. We previously reported that HFS, but not LFS, modulates astrocytic activation and induces release of glutamate and adenosine (Tawfik et al., 2010). Interestingly, HFS (higher than 50 Hz) failed to generate antidromic thalamocortical action potentials (Iremonger et al., 2006). Therefore, during HFS, the activation of the

thalamocortical neurons would not be long lasting but astrocytic activation would sustain and increase gliotransmitter release. In our clinical study, we found that adenosine release correlates with tremor reduction in a time-dependent manner (Chang et al., 2012). Adenosine inhibits neuronal firing in the thalamus through the activation of potassium channels (Pape, 1992) and decreases the amplitude of EPSP through the activation of A1 receptors (Bekar et al., 2008). Thus, astrocytic adenosine release evoked by HFS would be included as a part of DBS action. Finally, different responses to HFS of GABAergic interneurons and glutamatergic neurons would not be ruled out. In the hippocampus, GABAergic interneurons can generate sustained action potential without adaptation, but glutamatergic principal neurons cannot (Martina-Jonas, 1997). Also, moderate increase of potassium concentration significantly decreased the glutamatergic transmission, but not GABAergic transmission (Meeks-Mennerick, 2004). These different responses to HFS of GABAergic interneurons and glutamatergic principal neurons caused by voltage-gated Na^+ channel gating property may generate stronger inhibitory effects on postsynaptic cells and induce negative BOLD response. These may explain the reason of HFS-induced negative BOLD response.

HFS, but not LFS, increased BOLD activation in the contralateral cerebellum. Recent data indicate the presence of degenerative changes in the cerebellar Purkinje cell axons and dendrites in humans with ET (Erickson-Davis et al., 2010; Kuo et al., 2011; Louis et al., 2007; Louis et al., 2006). In addition, selective cerebellar lesions generated rhythmic tremor-like movement in an animal model (Wilms et al., 1999). These data suggest a role for the cerebellum in the pathological mechanism of tremor generation in ET and may also provide insight into the mechanism of tremor control by thalamic DBS.

Our data also demonstrate that HFS thalamic DBS modifies activity in the subcortical basal ganglia circuitry. The activation of these limbic structures may play a role in modulating both motor and non-motor functions. Recent clinical case studies showed that DBS at the ventral intermediated nucleus of the thalamus (VIM) improved not only tremor but also non-motor symptoms such as visuo-motor function, verbal memory, and mood (Fields et al., 2003; Lucas et al., 2000; Troster et al., 2003).

The pioneering research from Logothetis and colleagues has shown differential BOLD responses as a result of changing stimulation frequency, where LFS of the lateral geniculate nucleus (LGN) within the thalamus induced negative BOLD response in V1 area and HFS increased positive BOLD responses (Logothetis et al., 2010). As for comparing LGN data, the differences in cell types, input and output connections, and different type of stimulation electrode (microelectrode vs. quadripolar human DBS electrode) would not allow us to make a meaningful comparison. However, it is important to know that neural circuitry would be differentially modified by stimulation frequency even if the stimulation target area is the same.

We recognize several experimental limitations to this work. First the VIM thalamus, a substructure in VL that is the most popular DBS target for patients with ET, is not well defined in non-primate animals (e.g., rodent and swine). The VL thalamus is associated with more complicated functions and extensive areas of projection compared to the human VIM

thalamus. In the VL thalamus, multiple projections converge and diverge, including pallidal and cerebellar afferents (Gallay et al., 2008). Therefore, the VL thalamus in swine should be cautiously equated with the VIM thalamus in humans. In addition, due to current spread it is possible that adjacent thalamic nuclei, such as anterior thalamus and posterior thalamus, might have been affected in this study. Here, we increased the stimulation amplitude up to 7V, which is a very high amplitude rarely used in clinical DBS (1–5 V) (McIntyre et al., 2004). We did this to confirm the maximum stimulation effect using very high voltage both in 10 Hz and 130 Hz. However, it would be an experimental limitation, applying high amplitude stimulation rather than applying micro-step amplitude to see the detailed stimulation responses between 0 and 5 V. Lastly, although fMRI of awake animals might yield different results from those in the anesthetized state, our use of sedation and muscle relaxant was based on previous animal fMRI studies which showed robust visual and electrical stimulation-dependent BOLD responses and electrophysiological responses in the anesthetized state (Angenstein et al., 2009; Angenstein et al., 2010; Jin and Kim, 2010; Masamoto et al., 2007).

Conclusion

In the present study, we used a within-subjects design to investigate stimulation parameter-dependent effects of thalamic DBS on neural network activation. Our data suggest that DBS may dynamically and differentially modulate the activity in a network of interconnected areas in a stimulation parameter-dependent manner. Although the VL thalamus of swine is not complete homologue of the VIM thalamus in humans, these differential effects suggest that the VL thalamus may be an exemplary area for *in vivo* investigations of functional connectivity associated with the therapeutic and adverse effects of DBS. Finally, we suggest that the development of the swine model of essential tremor and performing a functional brain network imaging study during therapeutic DBS of this model would be a valuable future study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This work was supported by the National Institutes of Health (R01 NS 70872 award to K.H.L.), Mayo Foundation (2013–2015 Early Career Development Award to S.Y.C), Mayo CCaTS (2013 Transition Career Development Award to S.Y.C), and The Grainger Foundation. We also thank Michael P. Marsh for his technical assistance with the study.

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Abbreviations: BOLD, Blood oxygen level dependent; CB, Cerebellum; DACC, Dorsal anterior cingulate cortex; DBS, Deep brain stimulation; DPCC, Dorsal posterior cingulate cortex; FDR, False discovery rate; IC, Insular cortex; PFC, Prefrontal cortex; PRIMC, Primary motor cortex; PREMC, Premotor cortex; Stim, Stimulation.

Figure 1.

Low frequency and high frequency VL thalamic DBS induced BOLD changes. (A) areas of activation with VL stimulation at 5 V, 10 Hz, 90 μ s ($n = 5$) normalized to a 3D pig brain template. Significant activation ($FDR < 0.001$) was observed predominantly in the primary motor cortex (PRIMC), premotor cortex (PREMC), and prefrontal cortex (PFC); (B) event-related analysis of the average time course for each region of interest (PRIMC and PREMC) at 10 Hz and 130 Hz was plotted as average % change in BOLD signal across time ($TR = 3$ sec) using ten frames (30 seconds) prior to stimulation onset as the baseline. The vertical grey line indicates duration of stimulation. (C) areas of activation with unilateral VL stimulation at 5 V, 130 Hz, 90 μ s ($n = 5$); significant deactivation ($FDR < 0.001$) was induced in the ipsilateral premotor and PRIMC with activation in the ipsilateral PFC, insular cortex (IC), dorsal anterior cingulate cortex (DACC), and the contralateral cerebellum (CB). Abbreviations: BOLD, Blood oxygen level dependent; CB, Cerebellum; DACC, Dorsal anterior cingulate cortex; DBS, Deep brain stimulation, DPCC, Dorsal posterior cingulate cortex, FDR, False discovery rate; IC, Insular cortex; PFC, Prefrontal cortex; PRIMC, Primary motor cortex; Stim, Stimulation.

Figure 2.

Comparison of data from VL thalamus stimulation with different voltage intensities (3 V, 5 V, and 7 V) at 10 Hz and 130 Hz ($n = 5$). (A) all voltages showed regions of activation in the prefrontal, primary motor, and premotor cortices; however primary somatosensory cortex was activated only with 5 V and 7 V stimulations; (B) all voltages showed regions of activation in the prefrontal, primary somatosensory, insular cortices as well as areas of deactivation in the primary motor and premotor cortices. Additionally, contralateral cerebellum was activated with all of the voltages.

Abbreviations: BOLD, blood oxygen level dependent; CB, cerebellum; CC, cingulate cortex; DBS, deep brain stimulation; FDR, false discovery rate; IC, insular cortex; PFC, prefrontal cortex; PRIMC, primary motor cortex; PREMC, premotor cortex; V, voltage.

Figure 3.

Voltage dependence of VL thalamic DBS. (A) comparison of the time course for percentage change in the BOLD signal for specific regions of interest and with different voltage intensities (red: 3 V; purple: 5 V; blue: 7 V) at 10 Hz and 130 Hz. X-Y graphs demonstrate event-related time course of percent change in BOLD signal from baseline (y axis) vs. scan (x axis: TR = 3 sec) with 3 V, 5 V and 7 V at 10 Hz and 130 Hz (n= 5). Stimulation pulse width was 90 μ s.; (B) cluster size (mm^3) distribution comparing LFS with HFS in PFC, PRIMC, PREMC, PSS, SAC, and CB with 3 V, 5 V, and 7 V. With LFS, the cluster size increased with increasing voltage in the PFC, PRIMC, PREMC, and PSS. With HFS, the cluster size increased with increasing voltage in the PRIMC, PREMC, and CB; however, in

the PFC, PSS, and SAC, the volume of activated area increased from 3 V to 5 V, and decreased at 7 V.

Abbreviations: BOLD, Blood oxygen level dependent; CB, Cerebellum; DBS, Deep brain stimulation; PFC, Prefrontal cortex; PRIMC, Primary motor cortex; PREMC, Premotor cortex; PSS, Primary somatosensory cortex; SAC, Somatosensory association cortex.

Table. 1

Areas of Significant Brain Activation

Location	Cluster Size (mm)	Coordinates (x, y, z)	Max <i>t</i> -Score	Possible circuits involved
10Hz 5V 90µs				
Dorsolateral prefrontal cortex (I)	418	5.1, 33.8, 16.5	15.78	Cere-Th-Ctx loop (OC)
Primary somatosensory cortex (I)	413	14.4, 26.3, 15.5	15.34	Cere-Th-Ctx loop (OC)
Premotor cortex (I)	735	3.4, 28.0, 11.6	14.75	Cere-Th-Ctx loop (OC)
Primary motor cortex (I)	855	11.1, 24.8, 15.5	12.97	Cere-Th-Ctx loop (OC)
130Hz 5V 90µs				
Primary motor cortex (I)	339	5.3, 17.1, 24.9	-10.16	Cere-Th-Ctx loop (AC, OC), posterior VL-PRIMC
Premotor cortex (I)	292	1.6, 19.7, 15.6	-9.75	Cere-Th-Ctx loop (AC, OC), anterior VL-PREMC
Dorsolateral prefrontal cortex (I)	1113	4.3, 33.8, 16.4	15.56	Cere-Th-Ctx loop (OC)
Primary somatosensory cortex (I)	2399	13.7, 26.0, 14.6	15.34	PCS to the sensory thalamic area
Insular cortex (I)	1313	16.2, 25.3, 10.1	15.09	PCS to the sensory thalamic area
Dorsal anterior Cingulate cortex (I)	411	3.9, 28.0, 12.1	14.95	PCS to the sensory thalamic area
Somatosensory association cortex (I)	987	18.5, 12.3, 16.2	12.19	Cere-Th-Ctx loop
Dorsal posterior Cingulate cortex (I)	213	3.5, -6.8, 16.4	10.12	PCS to the sensory thalamic area
Putamen (I)	152	14.6, 19.0, 7.3	9.14	BGTC
Cerebellum (C)	133	-7.0, -20.5, 2.0	8.43	Cere-Th-Ctx loop (AC, OC)
Perirhinal cortex (I)	109	3.5, -5.5, 14.6	7.42	
Parahippocampal gyrus (I)	56	14.4, -3.3, -1.3	5.18	
Substantia Nigra	15	3.8, -0.5, -8.6	5.16	AC of BGTC (SNpr inhibits VL)
Caudate (I)	8	3.2, 24.9, 0.1	4.93	BGTC (reciprocally connection with VL)
Caudate (C)	6	-5.4, 12.6, 8.2	4.73	BGTC

** Areas showing with Bonferroni correction $P < 0.001$

Locations: I = Ipsilateral and C = contralateral. Coordinates (mm): x = mediolateral, y = rostrocaudal, and z = dorsoventral.

Abbreviations: AC, antidromic conduction; BGTC, Basal ganglia-thalamocortical; C, Contralateral; Cere-Th-Ctx loop, Cerebellothalamo cortical loop; Ctx, cortex; I, Ipsilateral; OC, orthodromic conduction; PCS, possible current spread; PRIMC, primary motor cortex; PREMC, premotor cortex; SNpr, substantia nigra pars reticulata; VL, Ventrolateral nucleus of the thalamus