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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-subject study of swine. Low (10 Hz) and high (130 Hz) frequency stimulation was applied at 3, 5, and 7 V in the VL thalamus of normal swine (n = 5). We found that stimulation frequency and voltage combinations differentially modulated the 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.

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 cerebello-thalamo-cortical pathway plays a crucial role in tremor suppression. However the reported brain activation sites and patterns of activity are inconsistent across such studies.

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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-subject 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). The VL thalamus is an element of the well-defined cerebello-thalamo-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: 36–37 °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 (10 Hz) and HFS (130 Hz) with three different amplitude intensities (3 V, 5 V and 7 V). 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/h, i.v.). To minimize geometric distortion, we set the EPI band-width 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 s) with 60 sec intervals (Min et al., 2012; Knight et al., 2013). The six conditions were tested in a fixed order, having 10 Hz (3 V, 5 V, 7 V) first, followed by 130 Hz (3 V, 5 V, 7 V). 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 s). 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., accepted for publication). 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 (ROIs) 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 a cluster size difference in % change (Min et al., 2012; Kim et al., 2013).