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Anterior Thalamic Deep Brain Stimulation: Functional Activation Patterns in a Large Animal Model

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ABSTRACT

Background: Deep brain stimulation (DBS) of the anterior thalamic nucleus (ATN) exerts its effects by modulating neural circuits involved in seizures. However, these networks remain incompletely characterized.
Objective: Investigate the effects of ATN DBS on network activity in a large animal model using 3-T fMRI.
Methods: Anesthetized swine underwent ATN DBS using stimulation parameters applied in the Stimulation of the Anterior Thalamus for the Treatment of Epilepsy (SANTE) trial. Stimulation amplitude, frequency, and temporal paradigm were varied and the resulting blood oxygen level-dependent signal was measured.
Results: ATN DBS resulted in activation within temporal, prefrontal, and sensorimotor cortex. An amplitude-dependent increase in cluster volume was observed at 60 Hz and 145 Hz stimulation.
Conclusion: ATN DBS in swine induced parameter-dependent activation in cortical regions including but not limited to the Papez circuit. These findings may hold clinical implications for treatment of epilepsy in patients with temporal or extratemporal seizure foci.

Introduction

While surgical resection of epileptogenic brain regions is the first option for treatment-refractory epilepsy patients, an estimated 40% of patients with localized epilepsy are not surgical candidates due to eloquence of the epilepsy onset zone. Increasingly, deep brain stimulation (DBS) is being considered as an alternative option, as it can modulate the epileptic network and is non-ablative. The anterior thalamic nucleus (ATN) is a DBS target in epilepsy due to its established connectivity within the Papez circuit and its widespread thalamocortical projections. The multicenter randomized double-blind Stimulation of the Anterior Nucleus of the Thalamus (SANTE) trial was recently conducted [1], in which ATN DBS resulted in a 40% decline in median seizure frequency after the blinded phase, and a 69% reduction after five years of unblinded follow-up [2]. While the mechanisms that mediate this therapeutic effect are not completely understood, it is known that ATN DBS exerts its effects, at least in part, by modulating mesial temporal circuitry. The anterior thalamus connects with hippocampus, parahippocampal gyrus and entorhinal cortex by way of both the cingulum bundle and the mammillothalamic tract and fornix: a network known as the Papez Circuit [3]. Indeed, both functional neuroimaging [4] and electrophysiological data [5] support the notion that DBS works by modulating networks distal to the site of stimulation, rather than simply inducing a local functional lesion. Our group has recently used functional magnetic resonance imaging (fMRI) in a swine model to investigate DBS in two other brain regions that have been targeted to treat epilepsy, the subthalamic nucleus [6] and centromedian nucleus of the thalamus [7]. Here, we used fMRI in swine implanted with ATN DBS to map the networks that may mediate the effects of this treatment.

Materials and methods

All study procedures were performed in accordance with the National Institutes of Health Guidelines for Animal Research and

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approved by Mayo Clinic Institutional Animal Care and Use Committee. The subject group consisted of three normal domestic male swine (30 ± 3 kg).

An MR image-guided Leksell stereotactic targeting system (Elekta, Stockholm, Sweden) modified for large animals was used for DBS electrode targeting and implantation [6]. Imaging was conducted by a 3-Tesla MR scanner (Signa HDx, General Electric, Fairfield, Connecticut) with a custom, in-house designed radiofrequency coil (Mayo Clinic, Rochester, Minnesota) [6]. Subjects were implanted with a quadripolar (contacts labeled 0, 1, 2, and 3) DBS electrode (Model 3389, Medtronic, Minneapolis, Minnesota). The electrode contacts were positioned such that contacts 0 and 1 were located within the left ATN on the basis of the pig atlas (Supplementary Fig. S1A) [8], with contact 0 residing in the same coronal plane as the mammillothalamic tract (Supplementary Fig. S1C). The location of the electrode was confirmed by a postsurgical computed tomography (Dual Source Somatom Definition, Siemens, Munich, Germany) scan (image resolution: 0.3x0.3x0.3 mm), which was co-registered to the pre-MRI magnetization prepared rapid acquisition gradient-echo (MPRAGE) scan (Supplementary Fig. S1B,C).

The fMRI experiment for each animal consisted of seven conditions (one run per condition) in which the stimulation frequency and amplitude were varied, with a 10 minute rest interval between each condition. During each run, unilateral bipolar stimulation (0–1+) was applied in a block paradigm (5 consecutive blocks of 6 sec ON, 1 min OFF) at 145 Hz, or 60 Hz; 90 μsec pulse-width; 2 V, 5 V, or 8 V. In addition, the temporal cycling paradigm used in the SANTE trial (145 Hz, 5 V, 90 μsec, 1 min ON, 5 min OFF) was applied in a single fMRI run consisting of two stimulation blocks. The

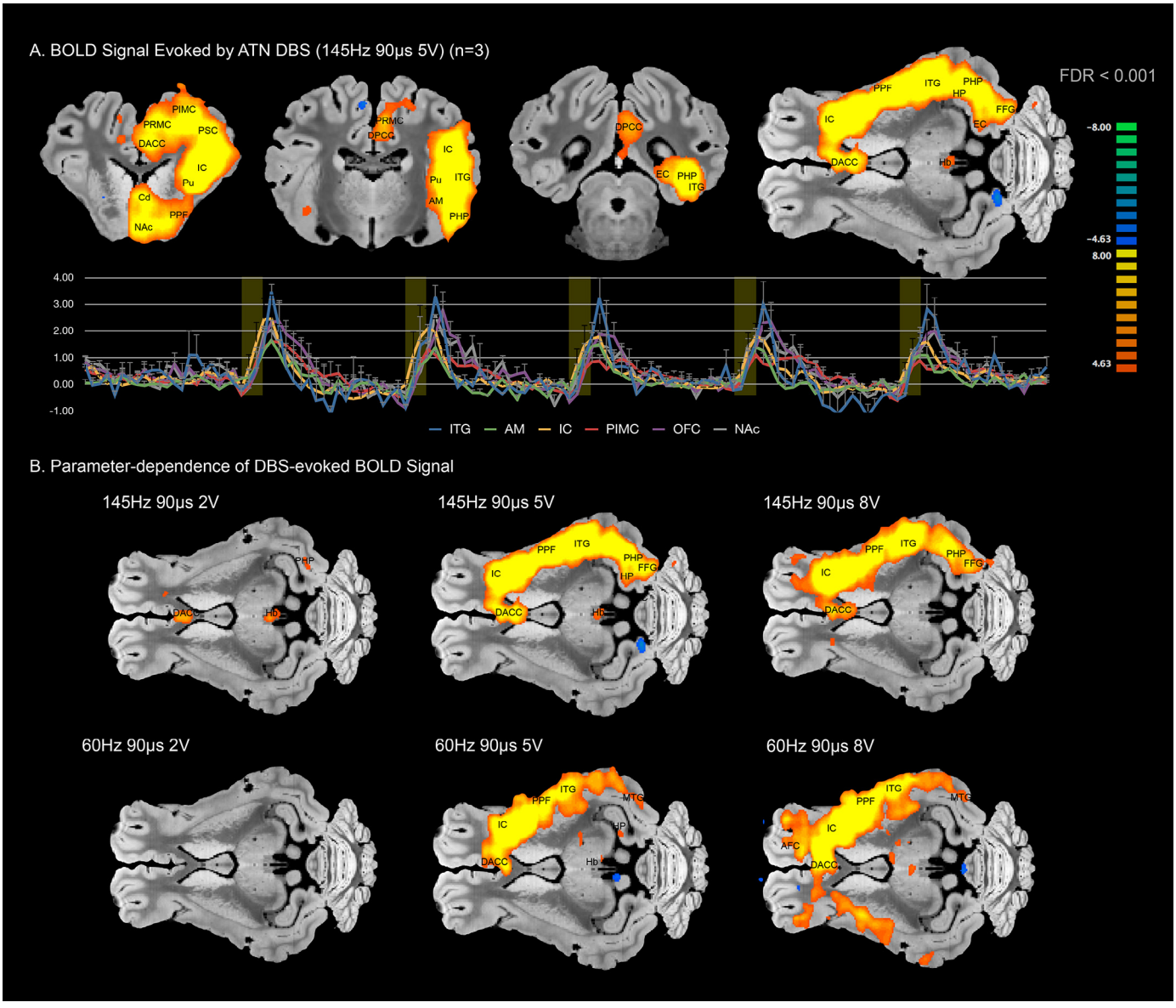

Figure 1. (A) Multi-subject functional activation map (n = 3) normalized with respect to a 3D pig brain template [9] showing areas activation resulting from ATN stimulation at 145 Hz, 90 μs, and 5V. Time course blood oxygen level-dependent (BOLD) signal data from select brain regions is shown below. (B) Multi-subject functional activation maps showing amplitude- (2V, 5V, and 8V) and frequency-dependence of DBS-evoked BOLD signal. Abbreviations: AFC: anterior frontal cortex; AM: amygdala; Cd: caudate; DACC: dorsal anterior cingulate cortex; DPCC: dorsal posterior cingulate cortex; EC: entorhinal cortex; FFG: fusiform gyrus; Hb: habenular nucleus; HP: hippocampus; IC: insular cortex; ITG: inferior temporal gyrus; MTG: middle temporal gyrus; NAc: nucleus accumbens; PHP: parahippocampal cortex; PIMC: primary motor cortex; PPF: prepyriform area; PRMC: premotor cortex; PSC: primary somatosensory cortex; Pu: putamen.