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Fornix deep brain stimulation circuit effect is dependent on major excitatory transmission via the nucleus accumbens

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ABSTRACT

Introduction: Deep brain stimulation (DBS) is a circuit-based treatment shown to relieve symptoms from multiple neurologic and neuropsychiatric disorders. In order to treat the memory deficit associated with Alzheimer's disease (AD), several clinical trials have tested the efficacy of DBS near the fornix. Early results from these studies indicated that patients who received fornix DBS experienced an improvement in memory and quality of life, yet the mechanisms behind this effect remain controversial. It is known that transmission between the medial limbic and corticolimbic circuits plays an integral role in declarative memory, and dysfunction at the circuit level results in various forms of dementia, including AD. Here, we aimed to determine the potential underlying mechanism of fornix DBS by examining the functional circuitry and brain structures engaged by fornix DBS.
Methods: A multimodal approach was employed to examine global and local temporal changes that occur in an anesthetized swine model of fornix DBS. Changes in global functional activity were measured by functional MRI (fMRI), and local neurochemical changes were monitored by fast scan cyclic voltammetry (FSCV) during electrical stimulation of the fornix. Additionally, intracranial microinfusions into the nucleus accumbens (NAc) were performed to investigate the global activity changes that occur with dopamine and glutamate receptor-specific antagonism.
Results: Hemodynamic responses in both medial limbic and corticolimbic circuits measured by fMRI were induced by fornix DBS. Additionally, fornix DBS resulted in increases in dopamine oxidation current (corresponding to dopamine efflux) monitored by FSCV in the NAc. Finally, fornix DBS-evoked hemodynamic responses in the amygdala and hippocampus decreased following dopamine and glutamate receptor antagonism in the NAc.
Conclusions: The present findings suggest that fornix DBS modulates dopamine release on presynaptic dopaminergic terminals in the NAc, involving excitatory glutamatergic input, and that the medial limbic and corticolimbic circuits interact in a functional loop.

Introduction

Deep brain stimulation (DBS) is a neurosurgical treatment for various neurologic and neuropsychiatric disorders, including Parkinson's disease, dystonia, major depression, and obsessive–compulsive disorder (Benabid, 2003; Benabid et al., 1991; Greene, 2005; Lozano et al., 2012). Recently, DBS has been applied within the medial limbic circuit (Papez circuit), to address memory deficits associated with dementia (Laxton et al., 2010; Ponce et al., 2015; Smith et al., 2012; Suthana et al., 2012). These early clinical studies indicated patient improvement in cognition, memory, and quality of life, and suggested that neural activity in memory-related circuitry might underlie this effect (Hardenacke et al., 2013; Lee et al., 2013).

The medial limbic circuit is one of the major pathways primarily involved in the cortical control of emotions and memory function (Rajmohan and Mohandas, 2007). This circuit includes the hippocampus (HP), fornix, mammillary body, anterior nucleus of the thalamus, cingulate cortex, parahippocampal gyrus, and entorhinal cortex (Mesulam, 2000). Within this circuit, the fornix is a major candidate brain target for DBS to treat memory impairment (Hescham et al., 2013; Laxton and Lozano, 2013). Specifically, in Alzheimer's disease (AD), it is proposed that fornix DBS influences memory recall by enhancing activity across distinct nodes involved in memory retrieval

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(Lee et al., 2013). One possible issue with fornix DBS arises from the diverse axons that travel through the fornix and terminate in distinct structures, including medial limbic and corticolimbic circuit components. The fornix has major input and output pathways from the HP and medial temporal lobe as well as the HP to the nucleus accumbens (NAc) that have known involvement in an array of cognitive processes (Kahn and Shohamy, 2013; Saint Marie et al., 2010). Although fornix DBS likely involves a wide range of axonal fiber effects, characterizing the electrical stimulation-induced response on neuronal communication beyond a few synapses is extremely challenging.

In place of a modular paradigm that views brain areas as independent processors, it is now accepted that dynamic functional connectivity among distributed neural nodes underlies many of the more complex neural functions (Bressler and Menon, 2010; McIntosh, 1999; Sporns, 2014). Communication between regions of the medial limbic and corticolimbic circuits, including the HP, NAc, amygdala (AM), and prefrontal cortex (PFC), are known to be critical for memory consolidation and retrieval (Badre et al., 2014; Carr et al., 2011; Hamann et al., 1999; Horner et al., 2015; Lisman and Grace, 2005; Schedlbauer et al., 2014). The ventral striatum in particular, which includes the NAc, is involved in cognitive control during memory retrieval (Scimeca and Badre, 2012; Speer et al., 2014). Moreover, functional MRI (fMRI) studies have shown that AD patients show decreased resting state activity in HP, PFC, and increased ventral striatum activity compared to age-matched controls (Buckner et al., 2005; Greicius et al., 2004; Zhou and Seeley, 2014). Together, these observations suggest that the inter-connected circuits play a distinct role in memory consolidation and retrieval, and are affected during memory dysfunction in AD.

In order to investigate the global circuit involvement during DBS, we have developed a technique that combines DBS and functional MRI (fMRI), as a means of tracing brain circuitry and testing the modulatory effects of electrical stimulation on a neuronal network (Knight et al., 2015; Min et al., 2014, 2012). Using this setup, we aimed to trace fornix DBS-induced global neural activity. Here, we measured the global blood oxygen level-dependent (BOLD) changes following different pharmacological manipulations and local dopaminergic neurotransmission in the NAc to determine the functional connectivity between the medial limbic and corticolimbic circuits following fornix DBS.

Experimental procedures

Experimental overview

Global and local changes associated with fornix stimulation were measured using three distinct experimental paradigms: (1) global hemodynamic changes using fMRI during fornix stimulation, (2) local neurochemical changes with fornix stimulation, and (3) global changes using fMRI pre- and post-NAc intracranial drug microinfusion. All experiments began with stimulating lead implantation in the fornix, followed by fMRI and intracranial drug microinfusions or carbon fiber microelectrode implantation and FSCV (Fig. 1A). In order to accurately and consistently implant the DBS electrode lead while minimizing inter-subject variability, high-resolution image-based targeting was performed as previously described (Min et al., 2012; Kim et al., 2013). The DBS electrode was implanted anterior and parallel to the medial portion of the fornix, in order to avoid penetrating the tract, as damage to these fibers is known to cause memory deficits (Laxton et al., 2010; Tsivilis et al., 2008; Vann et al., 2009; Wilson et al., 2008). To confirm that the target matched the final location of the electrode, post-surgical CT scans were co-registered with the pre-surgical magnetization prepared rapid acquisition gradient echo (MPRAGE) scan (Fig. 1C). For each subject, DBS lead contacts one and two were marked on the sagittal plane of the swine brain atlas (Fig. 1C) (Felix et al., 1999).

Subjects

All study procedures were performed in accordance with the National Institutes of Health Guidelines for Animal Research and approved by Mayo Clinic Institutional Animal Care and Use Committee. The subject group consisted of 17 normal healthy domestic swine (30 ± 3 kg). For all experiments, subjects received high-frequency electrical stimulation utilizing the parameters: biphasic 3, 5, or 7 V pulses at 130 Hz and pulse width of 150 μs (A-M System optical-isolated pulse stimulator Model 12,100, Sequim, WA, USA).

Stereotactic surgery

DBS electrode targeting and implantation was performed with an MR image-guided Leksell stereotactic targeting system (Elekta Inc., Stockholm, Sweden) modified for large animals (Min et al., 2012; Kim et al., 2013). A 3 Tesla MR scanner (General Electric Healthcare, Wakasha, WI; Signa HDx, 16× software) with a custom four-channel transmit–receive radiofrequency coil was used for preoperative anatomical imaging. 3D MPRAGE images were used for MR image-based targeting with swine brain atlas and COMPASS navigational software (modified for large animals) to determine the Leksell coordinates for stimulation target (Felix et al., 1999; Saikali et al., 2010; Shon et al., 2010).

Sedation was maintained with 1.5%–3% isoflurane during surgery and 1.5%–1.75% isoflurane during the fMRI and NAc dopamine recording experiments. Vital signs were continuously monitored throughout the procedures. Upon sedation, subjects were implanted with a quadripolar (contacts labeled 0, 1, 2, and 3) DBS electrode (Model 3389, Medtronic, Inc.). The electrode was positioned 2 mm anterior and parallel to the fornix unilaterally based on the brain atlas and anatomical landmarks (e.g., optic chiasm and mammillary bodies) to avoid a lesion in the white matter fibers of the fornix (Fig. 1B) (Laxton et al., 2010). The location of the electrode was confirmed through a post-surgical computer tomography (CT) (dual source Somatom definition, Siemens AG) scan (image resolution 0.6 × 0.6 × 0.6 mm) which was co-registered using a 6-parameter rigid-body transformation with the pre-surgical MPRAGE scan (Fig. 1C) (FSL, FM-RIB Analysis group) (Cho et al., 2010; Smith et al., 2004; Starr et al., 2002).

fMRI acquisition

Functional imaging was acquired with a custom six-channel transmit–receive radiofrequency coil using gradient echo-echo planar imaging (GRE-EPI): repetition time (TR) = 3000 ms; echo time = 34.1 ms; flip angle = 90°; frequency direction, R/L; field of view = 15 cm × 15 cm; matrix size = 64 × 64; axial slices 2.4 mm thick with no gap; slice number = 32; spatial resolution = 2.34 × 2.34 × 2.4 mm; scan duration = 390 s; 130 scans; integrated spatial spectral pulse was used for fat suppression. For anatomical registration, an additional single scan (GRE-EPI) was acquired in the identical orientation as the fMRI. After 5 volumes of discarded acquisitions to allow for scanner equilibrium, electrical stimulation was applied in a block paradigm with five six-sec-stimulation epochs interspersed with 1 min of rest, with 10 min of rest between scans.

fMRI post-processing and general linear model (GLM) analysis

A standard pre-processing sequence, including slice scan time correction, three-dimensional motion correction, temporal filtering (high-pass: Fourier basis set = 5 cycles, and low-pass: Gaussian filter, full-width at half-maximum = 3.1 s), and spatial smoothing (Gaussian filter with full-width at half-maximum = 1.1 pixels) was applied to each data set (Brain Innovation, BrainVoyager QX, Netherlands). Double-gamma hemodynamic response function (onset = 6 s, time to response peak = 11 s, time to undershoot peak = 21 s, response

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