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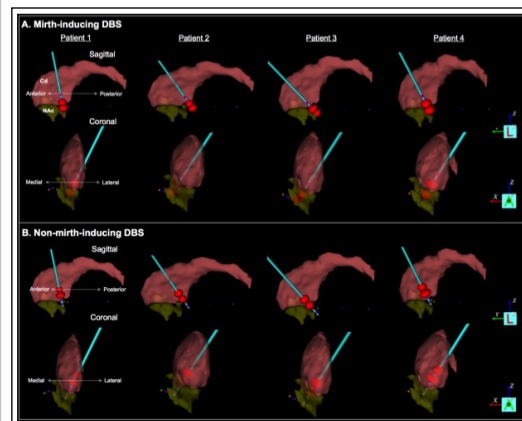
Introduction

Deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/Vs) is an investigational therapy for treatment-resistant obsessive-compulsive disorder. The ability of VC/Vs DBS to evoke spontaneous mirth in patients, often accompanied by smiling and laughter, is clinically well documented. However, the neural correlates of DBS-evoked mirth remain poorly characterized.

Methods

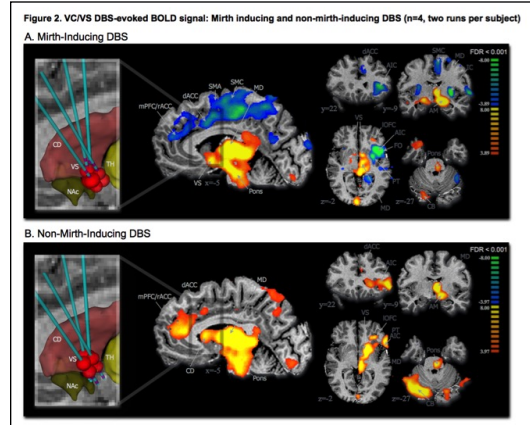
Patients undergoing VC/Vs DBS surgery underwent intraoperative evaluation in which mirth-inducing and non-mirth-inducing stimulation localizations were identified. Using dynamic causal modeling (DCM) for fMRI, the effect of mirth-inducing DBS on functional and effective connectivity among established nodes in limbic cortico-striato-thalamo-cortical (CSTC) circuitry was investigated.

Patient-specific models displaying the location of the VTA of the active DBS electrode during A) mirth-inducing and B) non-mirth-inducing DBS relative to the nucleus accumbens (NAc; green) and caudate (Cd; red).

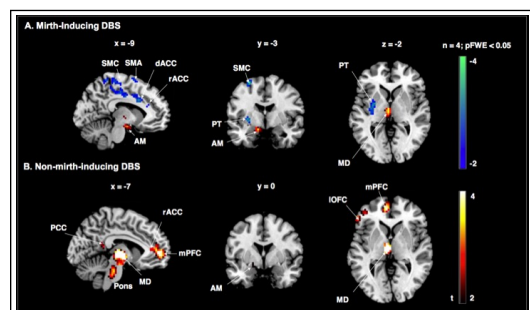


Results

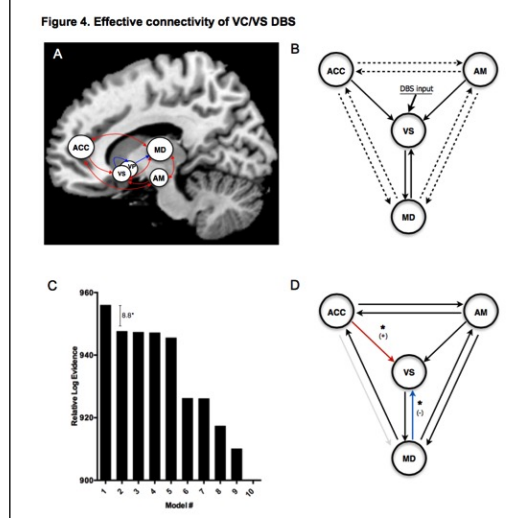
Both mirth-inducing and non-mirth-inducing VC/Vs DBS consistently resulted (conjunction, global null, familywise error-corrected p value < 0.05) in activation of amygdala, ventral striatum, and mediodorsal thalamus. However, only mirth-inducing DBS resulted in functional inhibition of anterior cingulate cortex. Dynamic causal modeling revealed that mirth-inducing DBS resulted in an attenuation of effective connectivity from both anterior cingulate and mediodorsal thalamus to ventral striatum relative to non-mirth-inducing stimulation.



VC/Vs DBS-evoked BOLD signal. A) Mirth-inducing DBS and B) Non-mirth-inducing DBS (n=4, two runs per subject for each DBS contact configuration) (multisubject analysis, false discovery rate-corrected p value < 0.001). Inset shows approximate location of the volume of tissue activated (red ellipsoids) by the active DBS electrode relative to subcortical structures including striatum (red), nucleus accumbens (green) and thalamus (yellow). Abbreviations: AIC = anterior insular cortex; AM = amygdala; CB = cerebellum (contralateral); CD = caudate; dACC = dorsal anterior cingulate cortex; IC = insular cortex; MD = mediodorsal thalamus; mPFC/rACC = medial prefrontal cortex/rostral anterior cingulate cortex; NAc = nucleus accumbens; PT = putamen; SMA = supplementary motor area; SMC = sensorimotor cortex; TH = thalamus; VS = ventral striatum



Multisubject conjunction analysis – Deep brain stimulation-evoked BOLD signal. A) Mirth-inducing DBS B) Non-mirth-inducing DBS; (familywise error-corrected p -value (pFWE) < 0.05 ; n = 4) AM = amygdala; dACC = dorsal anterior cingulate cortex; IOFC = lateral orbitofrontal cortex; MD = mediodorsal thalamus; mPFC = medial prefrontal cortex; PT = putamen; rACC = rostral anterior cingulate cortex; SMA = supplementary motor area; SMC = sensorimotor cortex



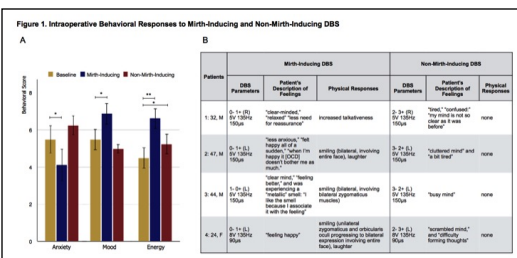
A) Established connectivity of the limbic cortico-striato-thalamo-cortical (CSTC) loop, with ACC and amygdala projecting to MD thalamus by way of ventral striatum (VS) and ventral pallidum (VP) (excitatory projection = red; inhibitory projection = blue). B) Simplified limbic CSTC loop that forms the basis of our model space, in which the inhibitory projections from VS to VP to MD are modeled as a single excitatory projection from VS to MD. C) The top ten models (fixed effects Bayesian model selection) and their respective log evidences relative to the least likely model. The winning model displayed log evidence of 8.8 greater than the closest competitor, corresponding to a posterior probability of $> 99.9\%$. D) The winning model determined by Bayesian model selection (* $p < 0.05$ indicates significant difference between mean interregional connectivity parameters (DCM B Matrix values): bootstrap random sampling with replacement)

Conclusions

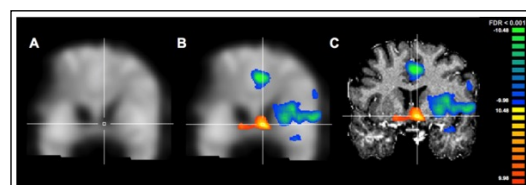
These results suggest that DBS-evoked mood elevation is accompanied by distinct patterns of limbic thalamocortical connectivity. Using the novel combination of DBS-evoked mood alteration and functional MRI in human subjects, we provide new insights into the network-level mechanisms that influence affect.

References

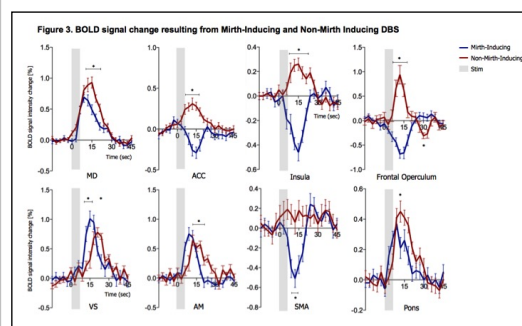
Gibson WS, Cho SH, Abulseoud OA, Gorny KR, Felmlee JP, Welker KM, Klassen BT, Min HK, Lee KH. The Impact of Mirth-Inducing Ventral Striatal Deep Brain Stimulation on Functional and Effective Connectivity. *Cereb Cortex* 2016; pii: bhv074.



A) Average changes in patient-reported anxiety, mood, and energy levels during DBS * $p < 0.05$, ** $p < 0.01$ (paired t test). B) Stimulation parameters and observed behavioral responses for each patient



A) A coronal slice from a T2*-weighted echo planar image (EPI) in a representative patient (#2), showing bilateral susceptibility artifacts due to DBS electrodes and unilateral artifact due to subgaleal connectors over the parietal cortex. B) Single-subject statistical map of BOLD signal overlaid on the EPI image. Crosshairs are located at the peak voxel within the ventral striatum. C) The same statistical map overlaid on the anatomical MP-RAGE image from patient 2



BOLD signal change resulting from mirth-inducing and non-mirth-inducing DBS at peak regions of DBS-evoked activation (two sample t test, $n=40$ stimulations per group, two sample t test with Holm-Sidak correction for multiple comparisons, $\alpha = 5.0\%$)