Difference between Nucleus Accumbens Core and Shell using Deep Brain Stimulation through functional Magnetic Resonance Image in rat

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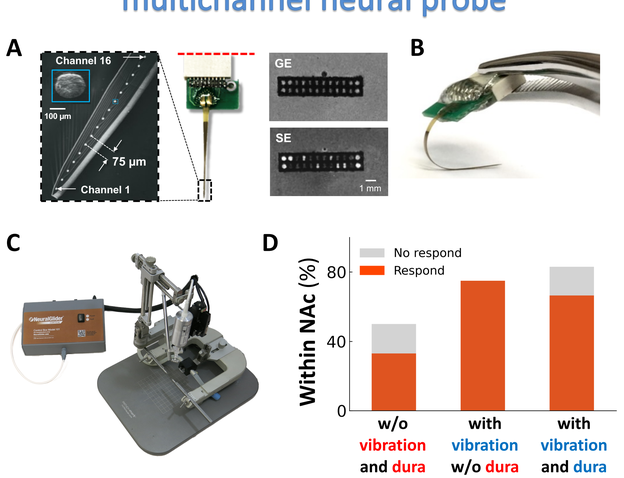
Introduction

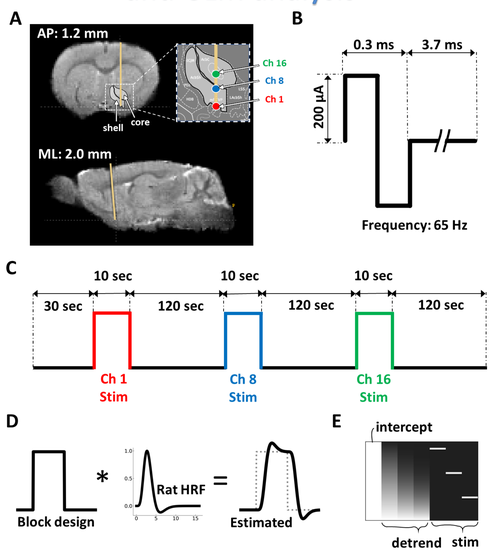
- **The nucleus accumbens (NAc)** has a significant role in the cognitive processing of motivation, addiction, reward and reinforcement.[1–4]
- **Simultaneous Deep Brain Stimulation (DBS)-fMRI** is a powerful tool for mapping functional connectivity and exploring neuromodulatory mechanism of DBS in vivo.[5-6]
- **By using MR-compatible and flexible multichannel neural probe** we performed site-selective stimulations of NAc to dissect the functional networks of its core and shell sub-structures. Such advantages allows systematic and functional in vivo study of differences between NAc core and shell.

MR-compatible and flexible multichannel neural probe



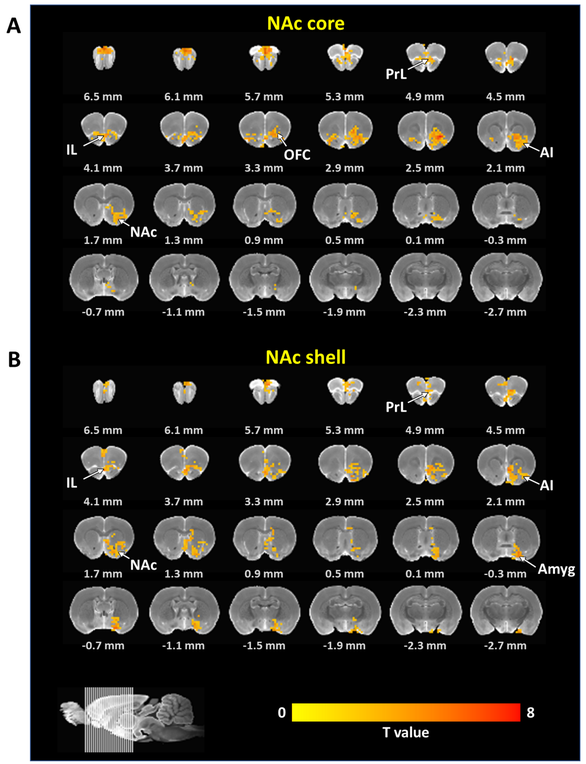
MR-compatible Multichannel neural probe and ultra
(A) An image presenting channel distance (75 um) and gross view of our MR-compatible multichannel neural probe, maximum projection MR image of our neural probe under spin-echo (SE) and gradient-echo (GE) sequences
(B) The flexibility of the neural probe
(C) Neuralglider™ inserter, which applies micron-scale, ultrasonic vibration during insertion. Among 20 rats, 6 rats didn't use the inserter for control and others used.
(D) Success rate of targeting NAc and activating in fMRI. Each group consists of 6 (control – no vibration), 8 (vibration without dura), 6 (vibration with dura); Female Sprague Dawley Rat (n=11), body weight 300g ~ 350g

Stimulation paradigm and GLM analysis



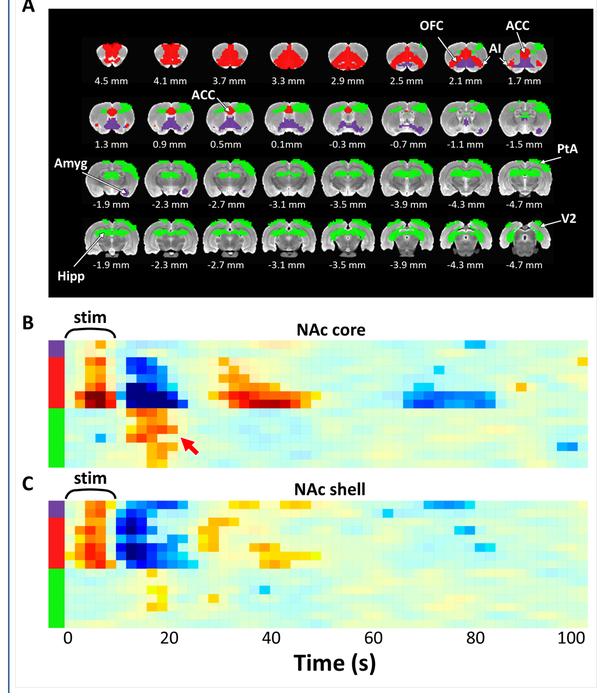
Neural probe implantation and stimulation paradigm
(A) Schematic illustration of the location of neural probe implantation. The 16-channel neural probe inserted across NAc core/shell (AP: 1.2 mm, ML: 2mm).
(B) Functional electrical stimulation parameters: biphasic pulse, frequency: 65Hz, current density: 200uA, duty cycle: 7.5%;
(C) Stimulation paradigm that used in this study. Three regions were selectively stimulated at different timepoints.
(D). Application of the generalized linear model (GLM) to functional magnetic resonance imaging (fMRI) data. Internal variables derived from the model[7] are converted into a time series and convolved with a hemodynamic response function. [7] This GLM is fitted at each voxel in the brain.
(E) Single-subject fMRI design matrix. Detrending 3rd order polynomial curve and yielding 1st level analysis with stimulation block.

NAc core vs NAc shell



NAc core and shell activation map
(A) The electrode is positioned at the core and shell of NAc. Channel 1 and 8 are placed at the NAc shell and Channel 16 is placed at the NAc core. The DBS-evoked fMRI results indicated that the shell of NAc appears to have a strong connection with medial prefrontal cortex (mPFC), anterior cingulate and amygdala.
(B) Bilateral mPFC, prelimbic cortex (PrC), infralimbic cortex (IL), orbitofrontal cortex (OFC) and anterior insula (AI) response to the core stimulation.

Impact to Intrinsic Functional Network



The network modulation effects NAc core stimulation
(A) Manually determined regions of interests (ROIs) based on DBS-fMRI activity map and Paxinos and Watson's rat brain atlas.
(B) Heat map presenting group-level pattern of oscillation of each ROI after stimulation. (p< 0.05, FDR corrected) PrL; prelimbic cortex, IL; infralimbic cortex, Amyg; amygdala, ACC; agnesis of corpus callosum, OFC; orbitofrontal cortex, AI; anterior insula, Hipp; hippocampus, PtA; pericollicular tegmental area , V2; secondary visual cortex

Discussion and Conclusion

- With our NAC-DBS, we have successfully separated the different networks of the NAc core and the shell.
- The network of the NAc core could be mapped through DBS-fMRI as revealed in previous studies. [8,9] The coactivation of OFC, IL by NAc core stimulation leads to AI stimulation is shown its functional relationship with cognitive process. [9]
- The network of NAC shell shows the coactivation of Amygdala and other areas. This indicates its functional relationship with reward-behavior as the previous study.[10]
- The time-lock analysis of DBS onset point shows the stimulation of NAc core triggered a large-scale network like default mode network (DMN) in a time-delayed manner. But the stimulation of NAc shell didn't show this tendency.
- Our DBS-fMRI approach using multichannel MR-compatible electrode is expected to be useful tool to study the DBS therapeutic mechanism and to understand side-effects caused by off-targets.

References: [1] Mogenson, G. J., Jones, D. L. & Yim, C. Y. *Prog. Neurobiol.* 14, 69–97 (1980). [2] Soares-Cunha, C. et al. *Mol. Psychiatry* 3241–3255 (2019). [3] Wenzel, J. M., Rauscher, N. A., Cheer, J. F. & Oleson, E. B. *ACS Chem. Neurosci.* 6, 16–26 (2015). [4] Calipari, E. S. et al. *Proc. Natl. Acad. Sci. U.S.A.* 113, 2726–2731 (2016). [5] Lai, H. Y., Younce, J. R., Albaugh, D. L., Kao, Y. C. J. & Shih, Y. Y. I. *Neuroimage* 84, 11 (2014). [6] Min, H. K. et al. *Neuroimage* 63, 1408–1420 (2012). [7] Lambers H, et al. *NeuroImage* 208, 116446 (2020) [8] Roger-carter MM et al, *J Neuroscience,* 39(44):8717– 8729 (2019) [9] Sesia, T. et al. *Exp. Neurol.* 214, 135–139 (2008). [10] Le H. et al. *Proc. Natl. Acad. Sci. U.S.A.* 109 (10) 3979-3984 (2012)

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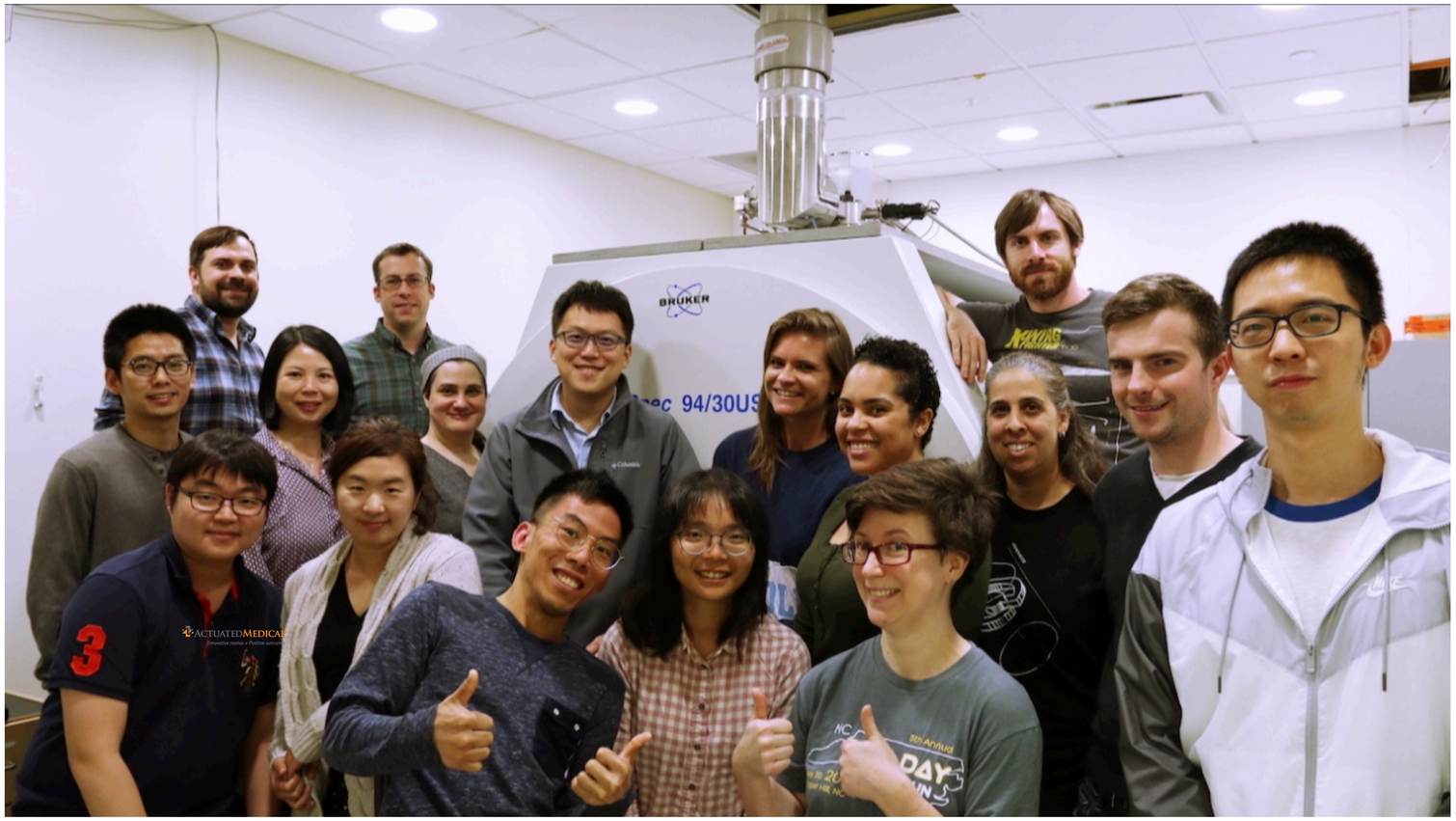

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