New Technologies for Molecular Imaging of Brain Function

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Comprehensive analysis of brain function depends on understanding the dynamics of diverse neurophysiological processes over large tissue volumes in intact animals and humans. Most existing approaches to studying the living brain suffer from limited tissue penetration, poor resolution, or lack of specificity for well-defined neural events. By combining molecular probes with noninvasive readouts, molecular imaging methods offer unique potential to map the brain in mechanistic detail. My presentation will begin with an overview molecular imaging approaches to measuring biological phenomena in the brain. I will briefly introduce the principal molecular imaging modalities and illustrate several recent advances at the forefront of technology development and biomedical applications.

In the second part of my talk, I will discuss my lab's work on molecular imaging of brain activity. We have introduced a novel brain mapping strategy that achieves a combination of molecular specificity and comprehensiveness using a novel MRI-based functional imaging technique, in which neural processes are studied using MRI-detectable sensors for signaling molecules in the brain. I focus particularly on contrast agents designed to detect neurotransmitters and on genetically encodable sensors for intracellular signaling. In our neurotransmitter imaging approaches, we used protein engineering to generate contrast agents that allow the monoamines dopamine and serotonin to be measured by MRI. We combined the dopamine sensor with brain stimulation techniques to map signaling patterns in the ventral striatum of rats (**Figure 1**), and are trying to understand how these patterns relate to stimulus properties and to readouts obtained using conventional functional MRI. Using the serotonin sensor, we are mapping neurotransmitter reuptake processes and studying their modulation by pharmacological agents. Ongoing research aims at producing analogous neurotransmitter sensors with greater target sensitivity. Our work on genetically encodable sensors revolves largely around variants of endogenous iron storage proteins, which we have modified to produce MRI changes in response to kinase activity or calcium ion concentration changes. We have applied high throughput protein engineering approaches to improve sensitivity of these probes, and we demonstrate results with magnetically-enhanced proteins expressed in cells.

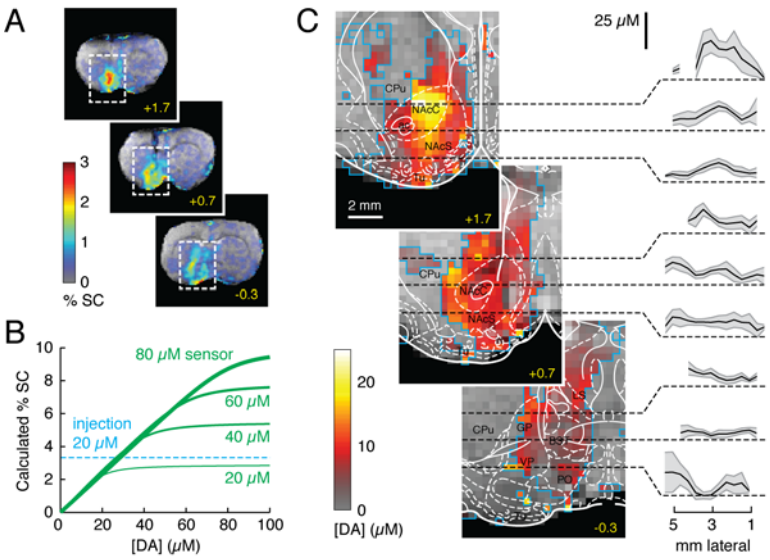

Figure 1. Quantitative functional molecular imaging of brain activity. (A) Raw maps of signal change averaged over seven animals injected with an MRI dopamine sensor and treated with reward-related stimuli. Distribution of percent signal change (%SC) over three coronal sections; rostrocaudal coordinates in yellow. **(B)** Calculated %SC as a function of released dopamine concentration ([DA]) for four sensor concentrations, showing linearity of %SC *vs.* [DA], except for saturation effects. In areas that received substantial contrast agent infusion, a ratio of 8 μM dopamine per %SC can be used to estimate dopamine concentrations. **(C)** Quantitative mapping of average peak dopamine concentrations over regions outlined in panel A. Blue outlines indicate voxels included in the analysis, each incorporating data from 2-7 animals. Rat brain atlas is overlaid with regions labeled in black. Plots (right) show means (black lines) and SEMs (shading) of dopamine concentrations along dashed lines in respective images.