BRAIN Initiative: Microscopic foundation of multimodal human imaging

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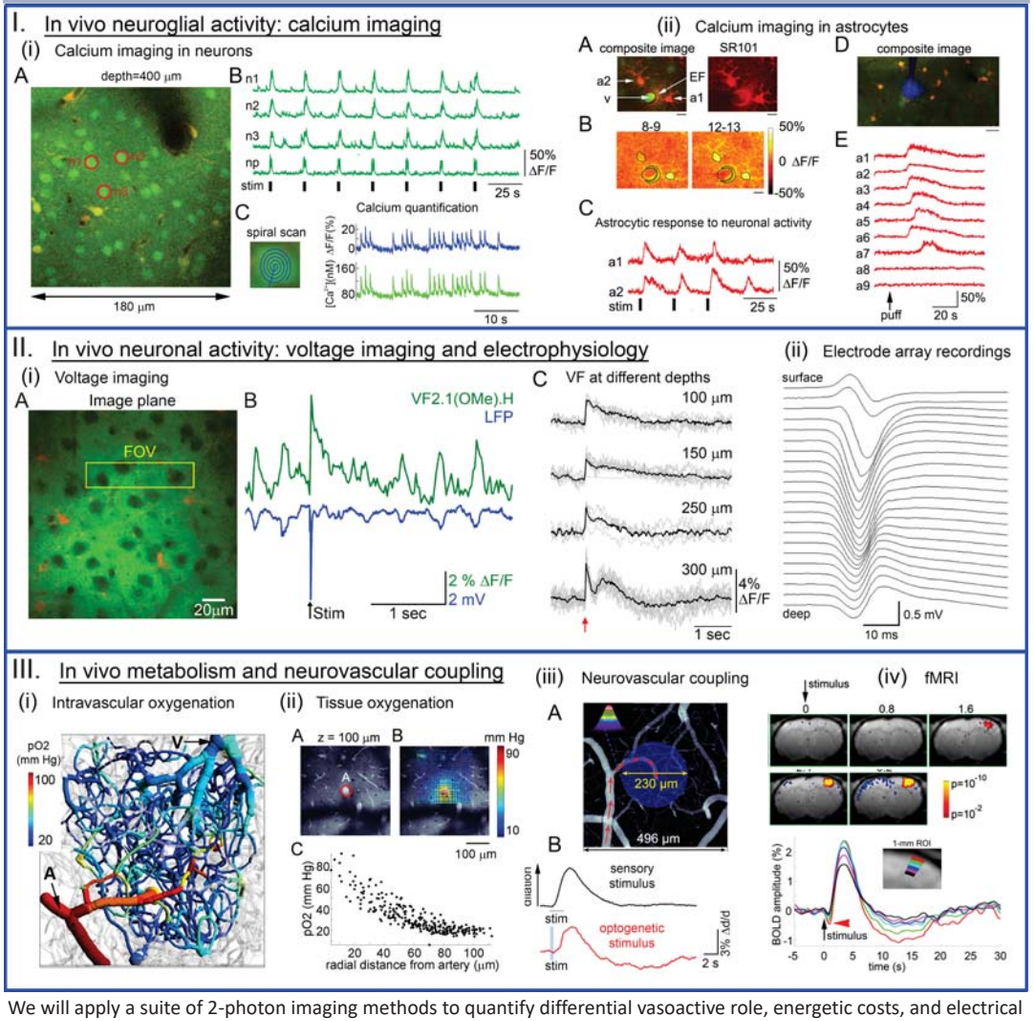
MICROSCOPIC MEASUREMENTS and MANIPULATION



We will apply a suite of 2-photon imaging methods to quantify differential vasoactive role, energetic costs, and electrical currents/potentials associated with activity of different neuronal cell types. These experiments will determine how activity of a particular type of neurons affects CBF, $CMRO_2$, and current dipole. Our 2-photon methods include high-resolution longitudinal measurements on neuronal activity (Ii, IIi), astrocytic reactivity/calcium surges (iii), intravascular/tissue oxygen availability and consumption (IIIi-ii), and others. These measurements will be combined with laminar and surface electrophysiological recordings (IIii). Selective stimulation of specific neuronal cell types will be achieved using optogenetics (IIIiii), both in optical and fMRI experiments (IIIiv). Mouse fMRI will provide a translational bridge and will be used for validation of the bottom-up modeling effort.

Acknowledgements

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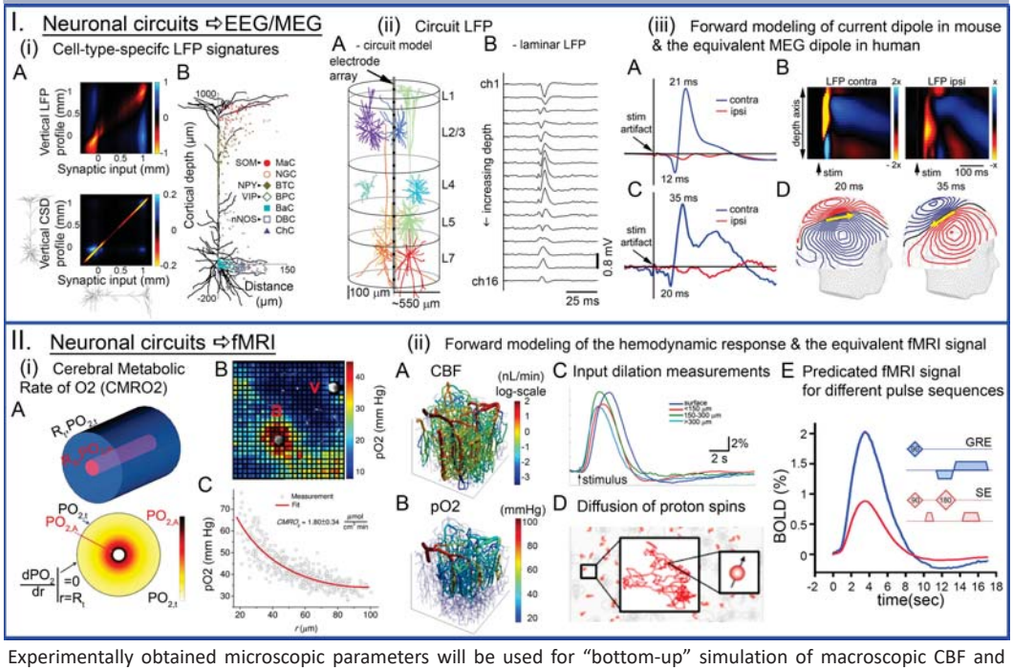
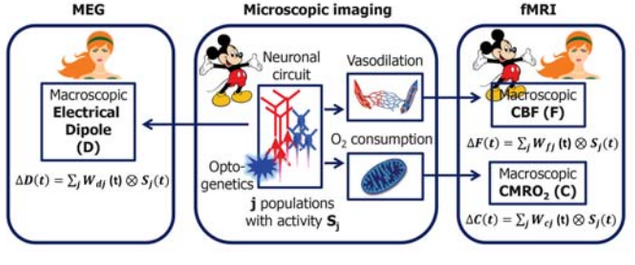
COMPUTATIONAL BRIDGES



Experimentally obtained microscopic parameters will be used for "bottom-up" simulation of macroscopic CBF and $CMRO_2$, that can be obtained noninvasively using calibrated BOLD fMRI, and current dipole moment, that can be obtained noninvasively using MEG. Top row: Projection domains of different types of inhibitory neurons segregate along Pyramidal cells producing dipoles (Ii). Their summed contributions can be detected by laminar recordings of extracellular potentials (Iii) that can be used to forward calculate MEG signals (Iiii). Bottom row: Knowing microscopic distributions of CBF and $CMRO_2$, we can calculate the corresponding BOLD fMRI signal.

THEORETICAL FRAMEWORK



Goal: explicitly estimate the cellular level of neuronal functional reorganization in human patients where we do not have access to microscopic measurements of any kind. All that we have is noninvasive measurements that can be thought of as "observations from a distance" of signals with indirect relationship to neuronal activity at the level of specific cell types.

The overarching idea is that the activation of different neuronal cell types has different signatures in the evoked CBF (ΔF), CMRO2 (ΔC), and the macroscopic current dipole responses (ΔD), and by measuring these responses noninvasively in the human brain we will be able to probe more deeply the underlying cellular and circuit activity.

For each neuronal population (e.g., excitatory and inhibitory), the current dipole moment (measured by MEG) and CBF/$CMRO_2$ (measured by calibrated BOLD) can be expressed as convolution of the neuronal activity for neuronal population of cell type ***j*** with time-resolved weighting factor ***W(t)*** for that cell type (that can be thought of as cell-type-specific impulse response function, IRF). The weighting factors ***W(t)*** will be determined experimentally using selective optogenetic activation of specific cell types in mice.