

Label-free Imaging of Tissue Dynamics in the Cortex using Spectral-Domain Optical Coherence Tomography

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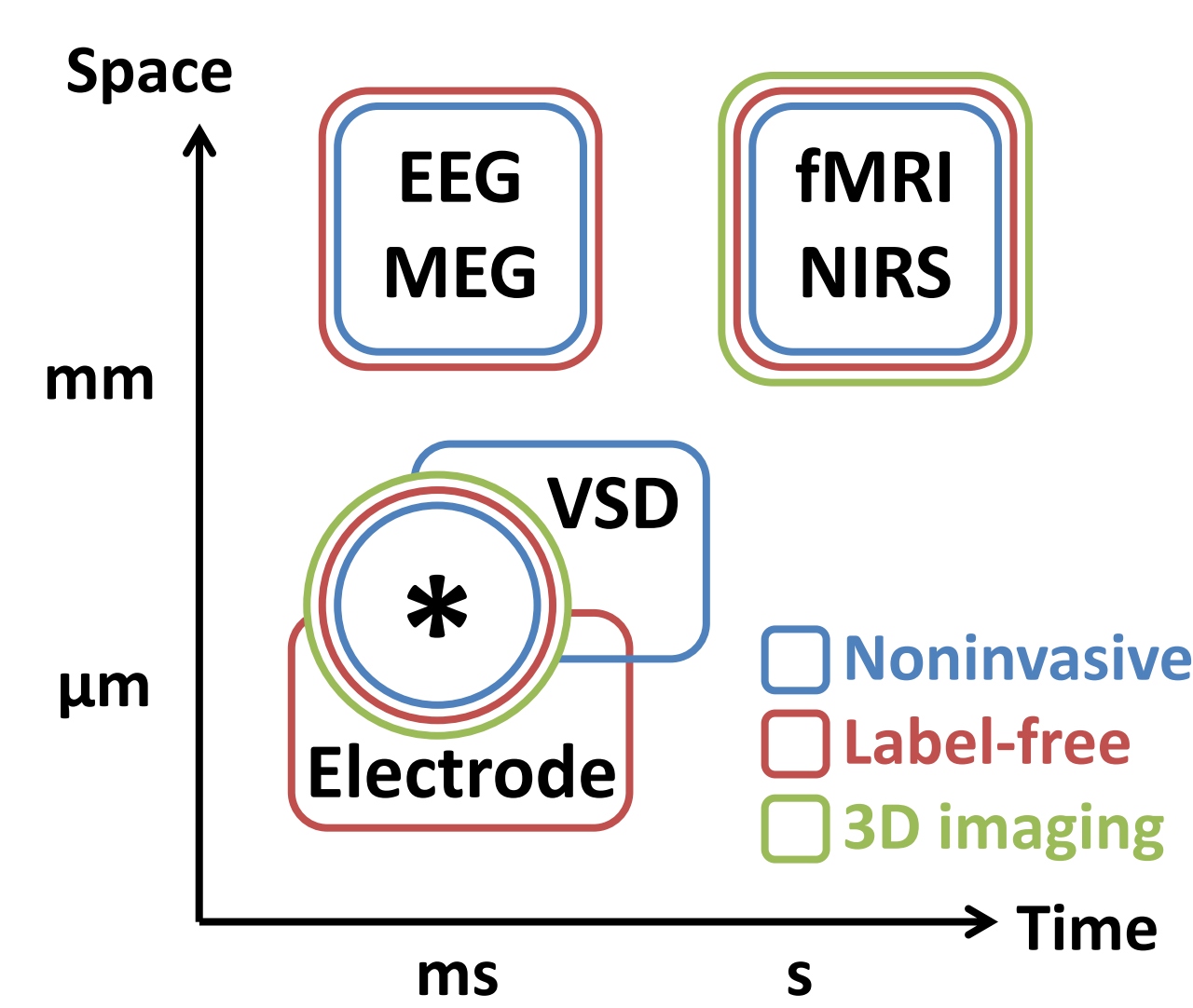
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INTRODUCTION

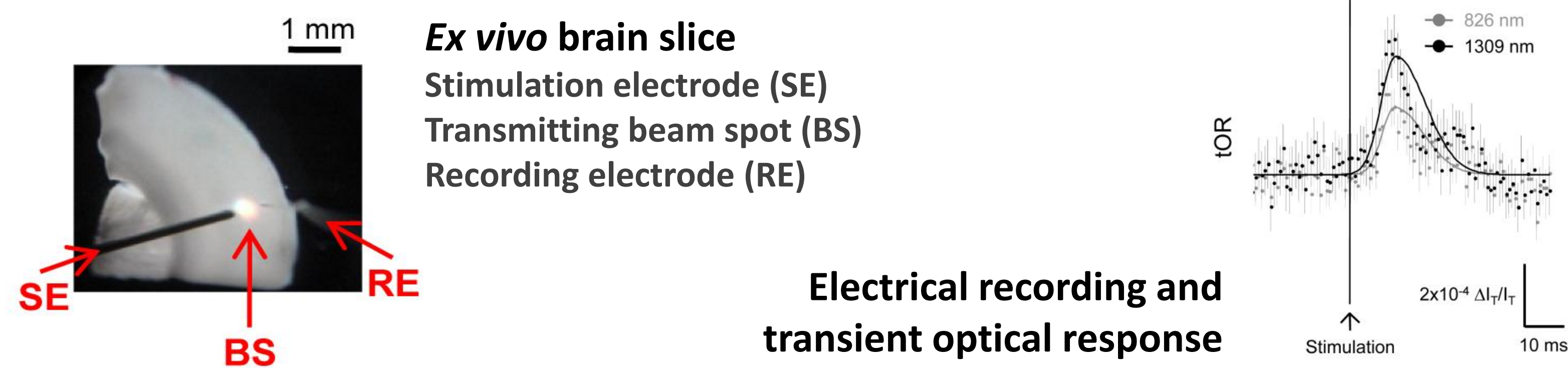
Functional Brain Imaging

Spatiotemporal imaging of brain activity has played a key role in studying human brain function. However, no conventional technology has provided a suitable tool for thorough monitoring of brain activity. Since the brain activity is fundamentally the ensemble of excitation of neuronal cells, one should be able to perform **noninvasive, label-free, and three-dimensional dynamic imaging of neural activity with μm and ms resolution** (* in the right figure). As a major milestone toward development of such a promising technology, this study utilizes spectral-domain optical coherence tomography (SD-OCT), and proposes a novel way to interpret the field reflectivity dynamics of tissue, speckle decomposition. It enables depth-resolved imaging of tissue dynamics during functional activation – hemodynamics and neural activity.



Transient Optical Response (tOR)

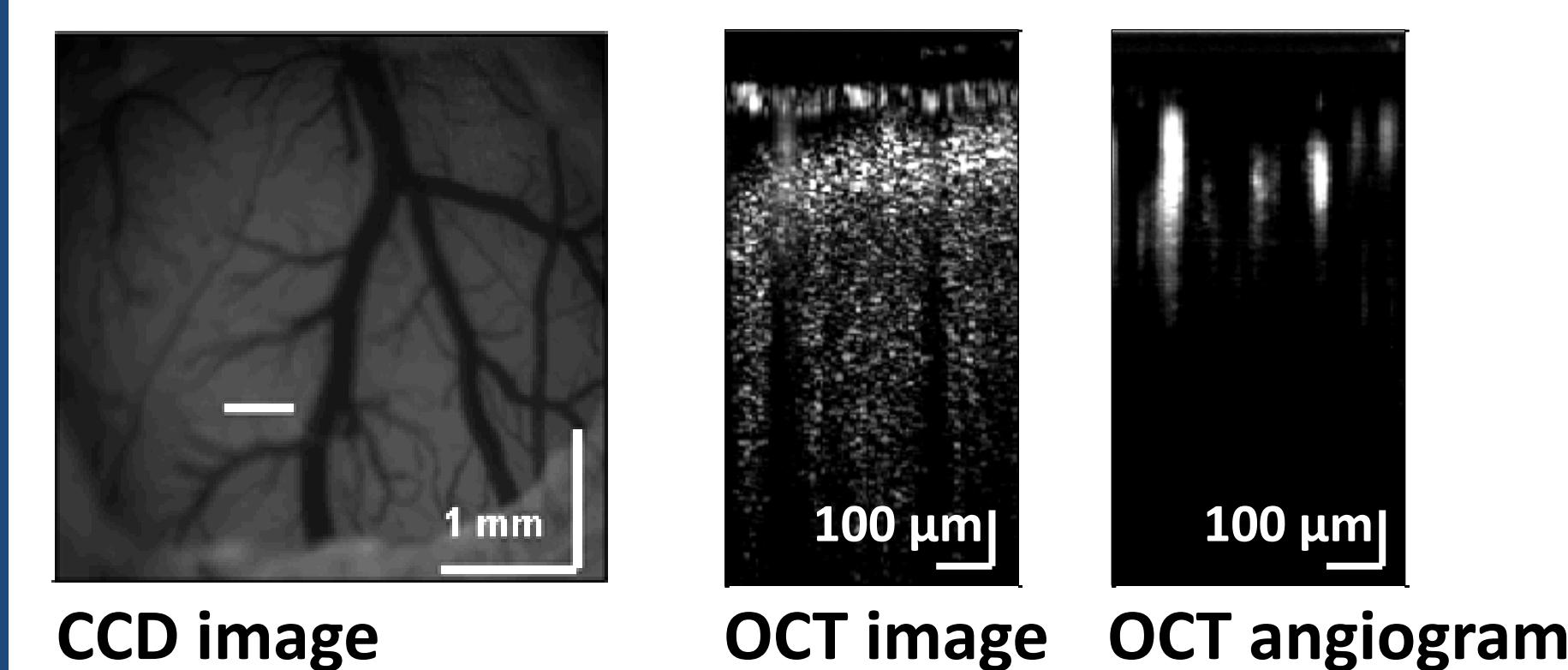
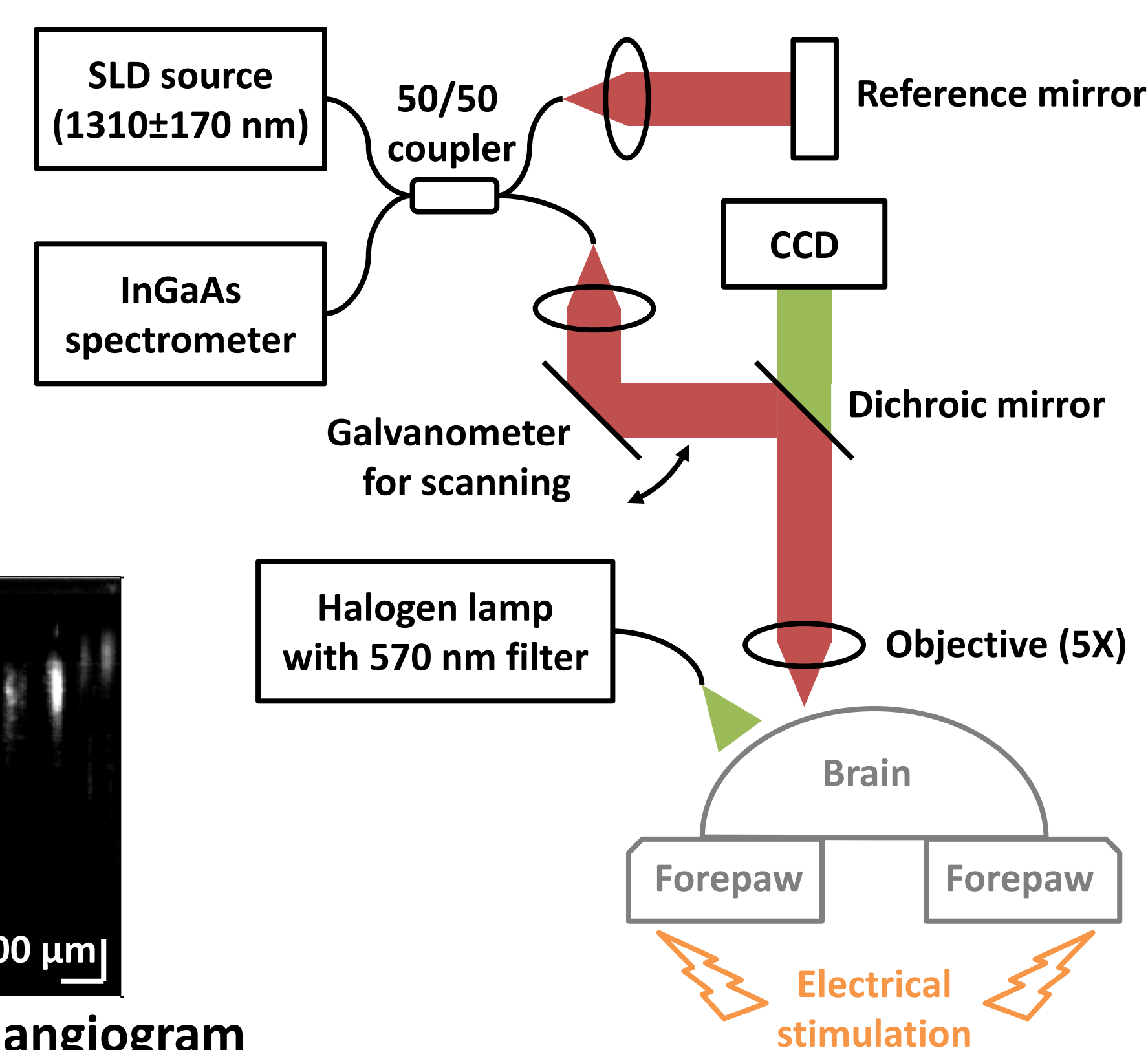
The rationale and feasibility of this approach have been supported by the author's previous work showing that the intrinsic transmittance of *ex vivo* brain tissue exhibits a localized and transient optical response with ms time scale during neural activation (J Lee et al., Neuroimage, 2010).



METHODS

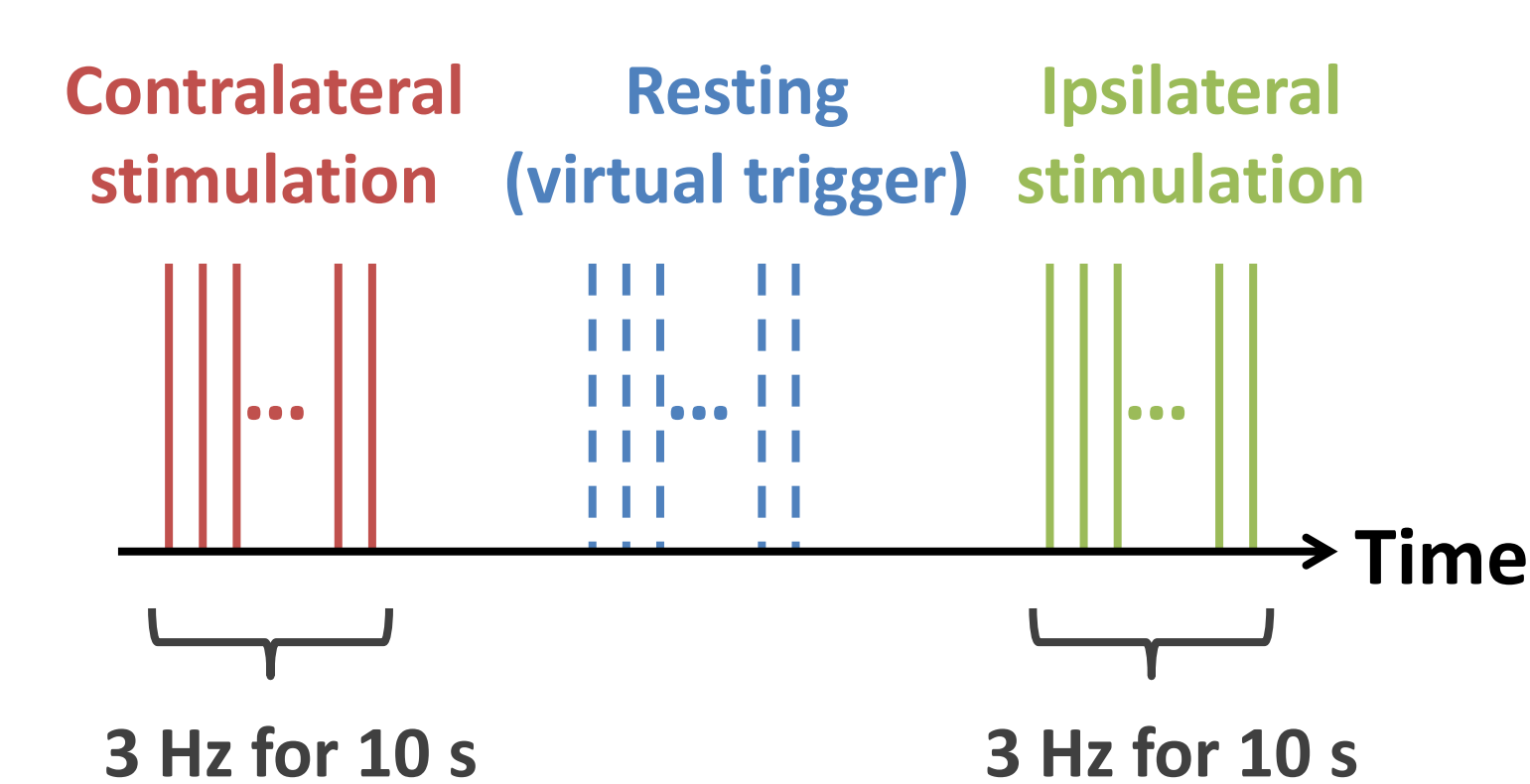
High-speed SD-OCT for *in vivo* Brain Imaging

An SD-OCT system has been developed and used for repeated scanning of the cross section of rat cortex during functional activation. This scanning produces high-resolution data of the spatiotemporal dynamics of the field reflectivity. 2-D scanning area: $1000 \times 500 \mu\text{m}$ (Z, X) Spatial resolution: $3.5 \times 7 \mu\text{m}$ Temporal resolution: 4 ms (250 area/s)



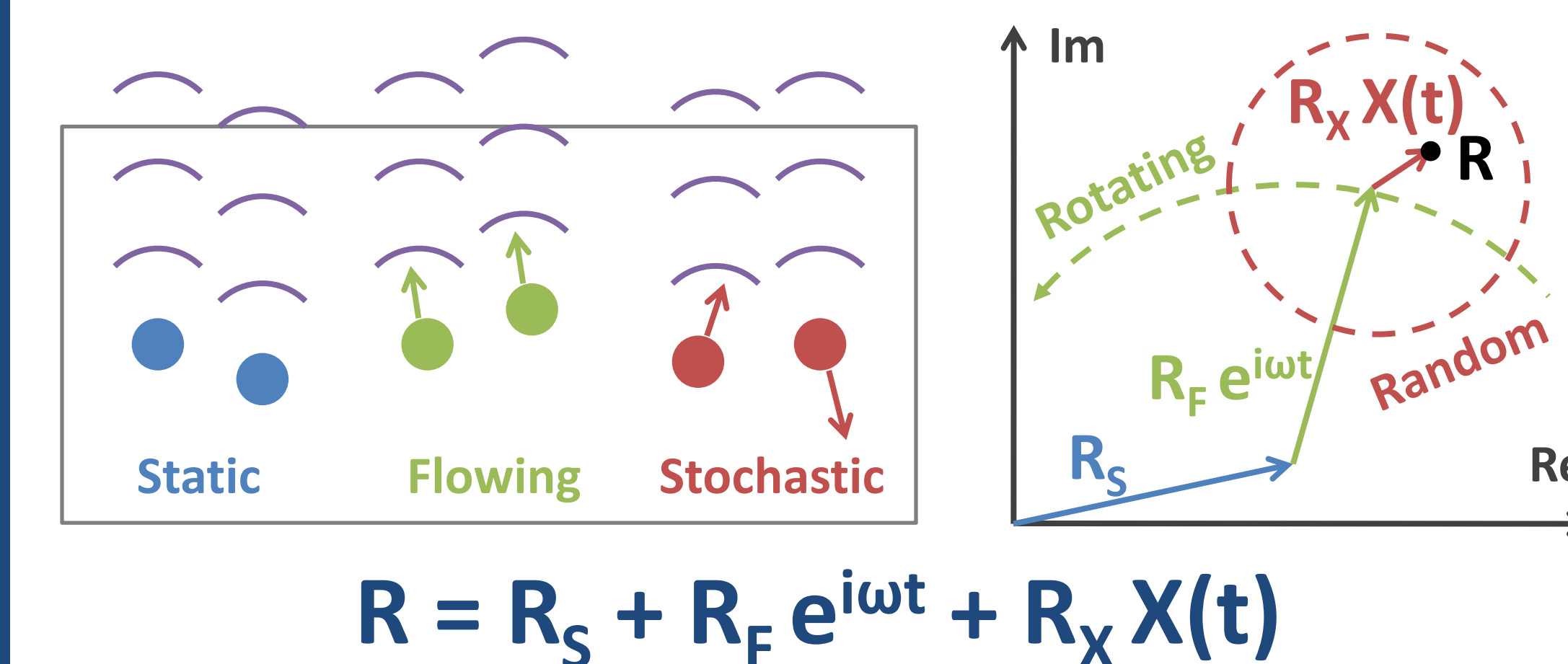
Animal Preparation and Functional Activation

Sprague-Dawley rats (250-350 g) were anesthetized with Ketamine. A hole (4 mm in diameter) was prepared through the skull, then the dura was carefully removed. An activated region was localized with ball electrode recording. A **cranial window** was equipped after localization. While the cortex was optically imaged, the contralateral forepaw was stimulated at 3 Hz for 10 seconds (30 trials). After recovery, the ipsilateral forepaw was stimulated.



SPECKLE DECOMPOSITION

Dynamics-based Decomposition of Three Components

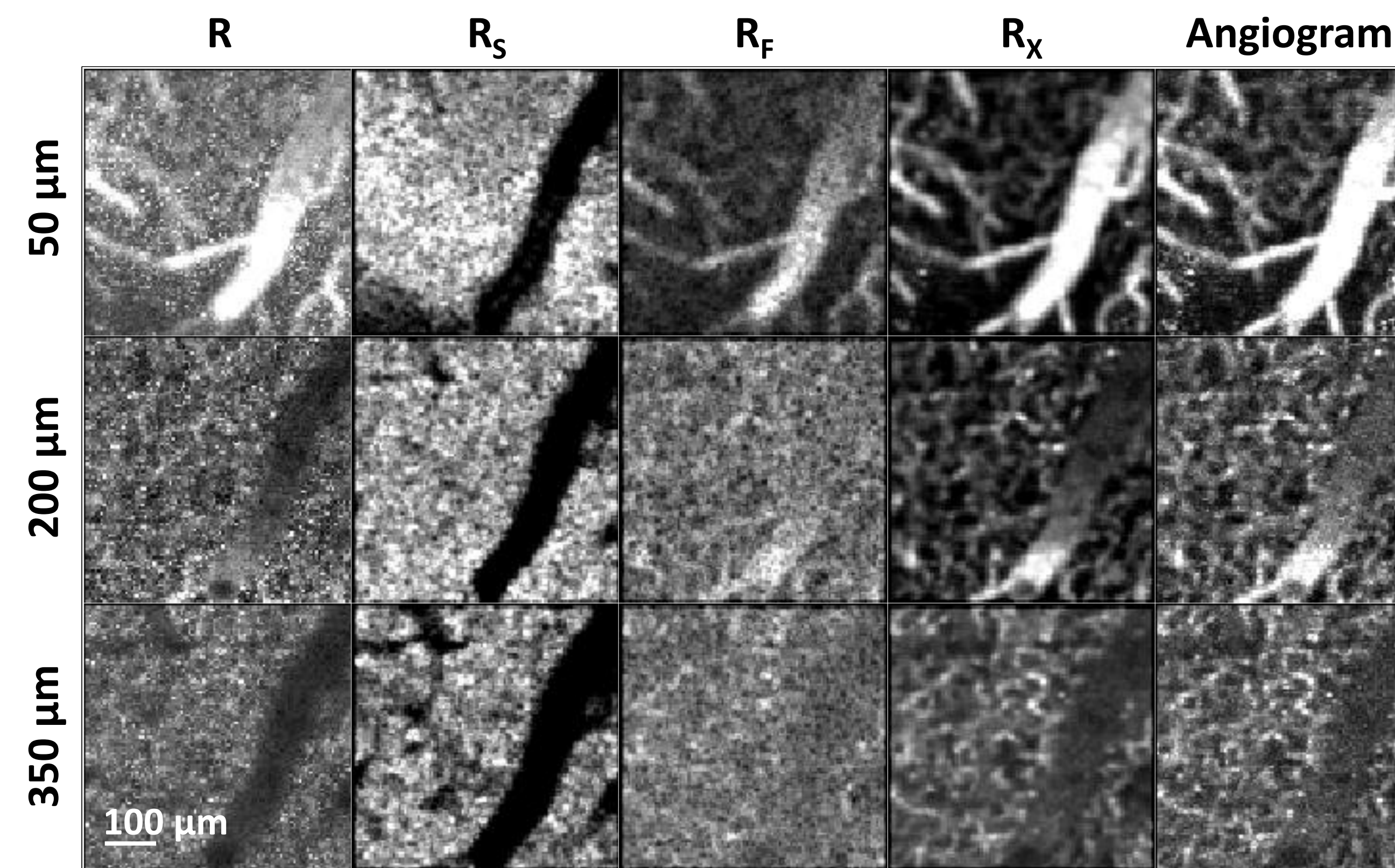


The field reflectivity of tissue shows a behavior such that each voxel consists of three groups of scatterers: **static, slowly-flowing, and stochastically-moving scatterers**. A novel analysis method, speckle decomposition technique, was developed to decompose those three components.

STRUCTURAL IMAGING

Tissue Structure (R_S) and Vessel Structure (R_X)

The map of the magnitude of R_S may contain information about tissue structure, while the map of the variance of stochastic component (R_X) reveals the vascular structure.

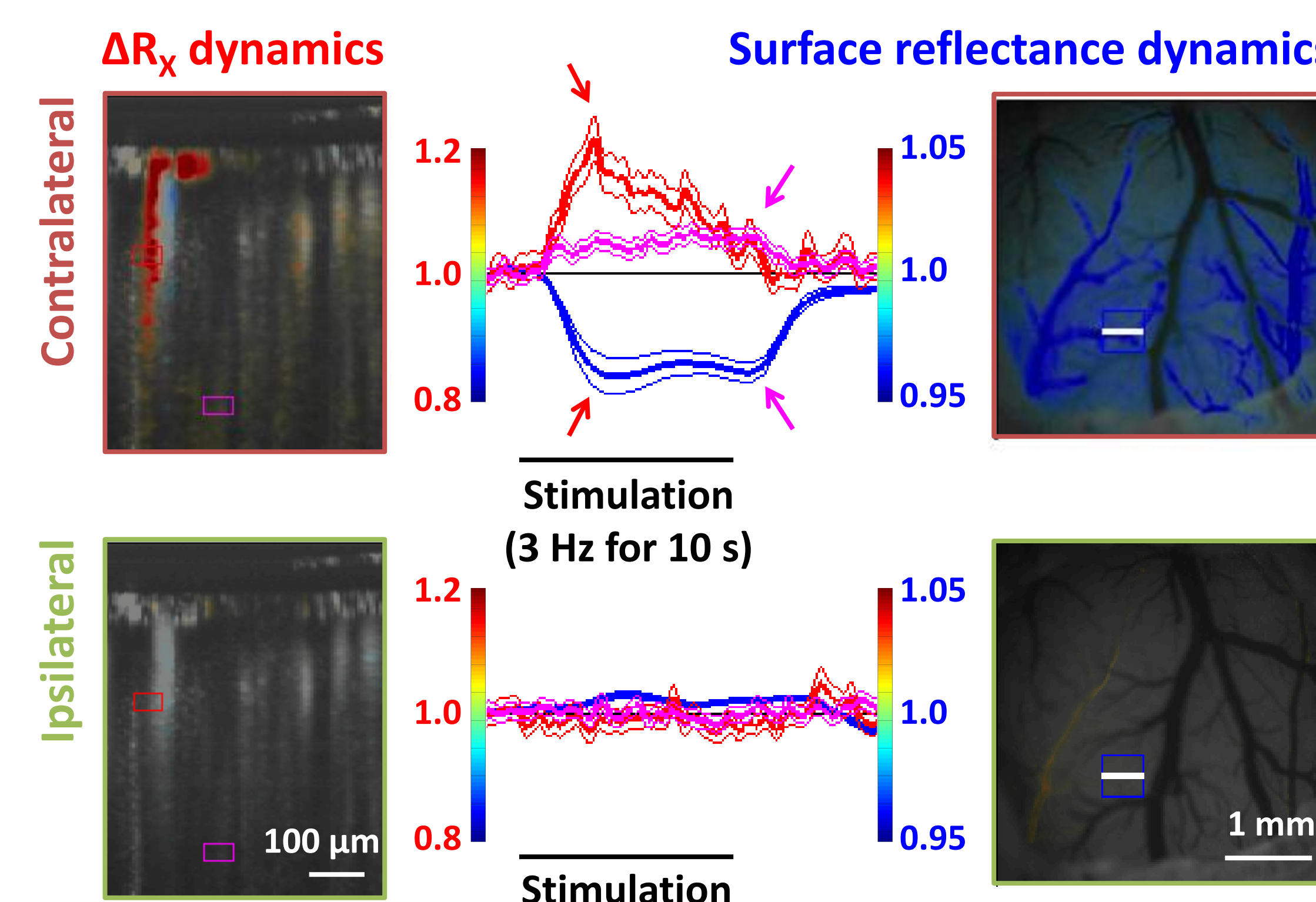


FUNCTIONAL IMAGING – HEMODYNAMICS

Depth-resolved Imaging of Hemodynamics ($\Delta R_X/R_X$)

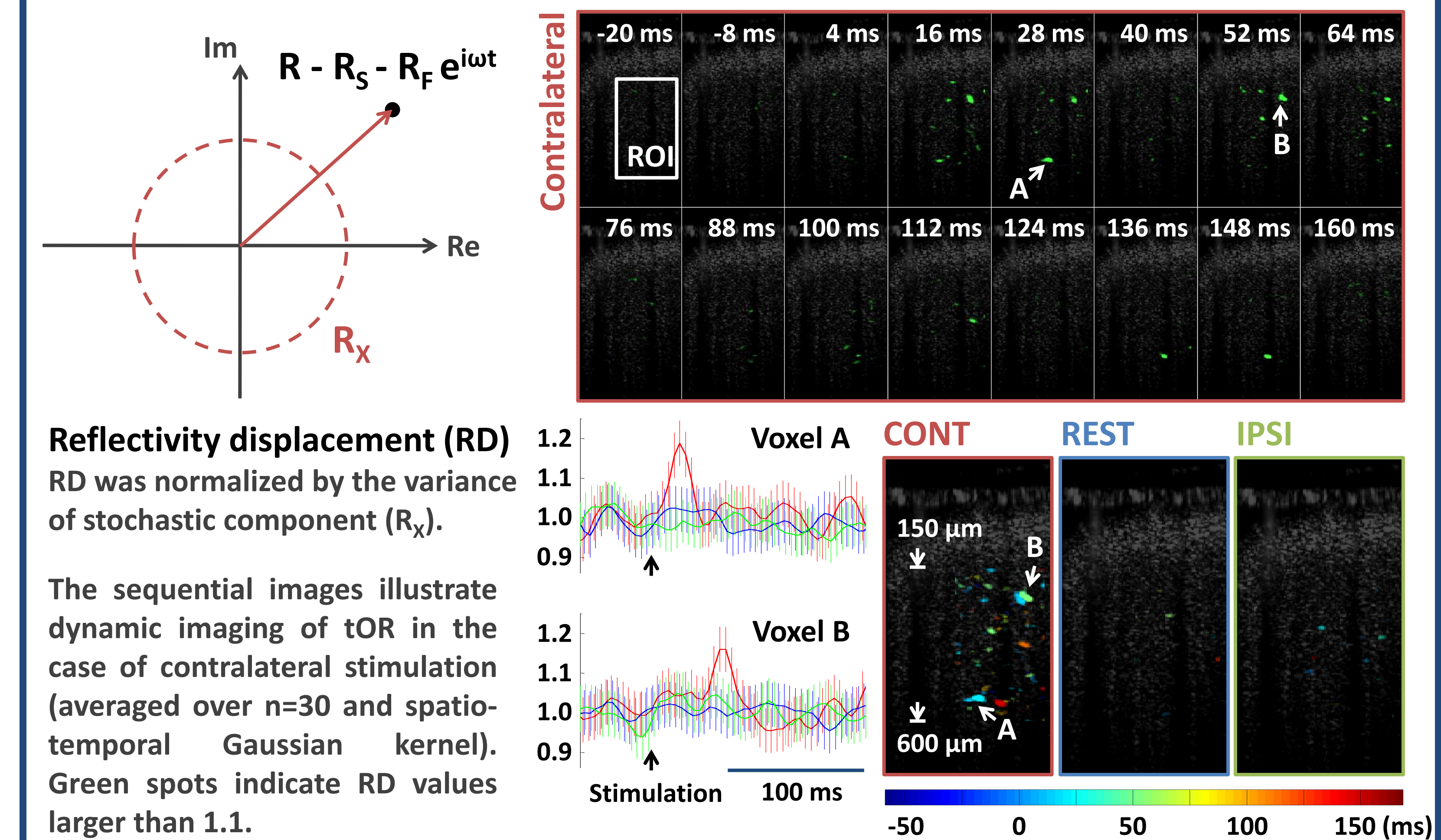
The variance of stochastic component (R_X) was monitored every 0.1 s during functional activation. The R_X exhibits a localized increase when the contralateral forepaw was stimulated. The R_X dynamics is similar to the dynamics of cortical surface reflectance that was simultaneously measured by the CCD. This result supports that the ΔR_X dynamics is closely related to the hemodynamic response. The ΔR_X and fractional changes in the surface reflectance are displayed as snapshots at 4 s after the onset of stimulation. Both dynamics result from averaging 10 blocks.

The time course of surface reflection likely consists of two components: rapidly increasing one (red arrow); and the one gradually increasing until the stimulation stops (magenta arrow). Comparing to the ΔR_X imaging, each component may be related to the response at surface vessels (red) and deep tissue (magenta), respectively.



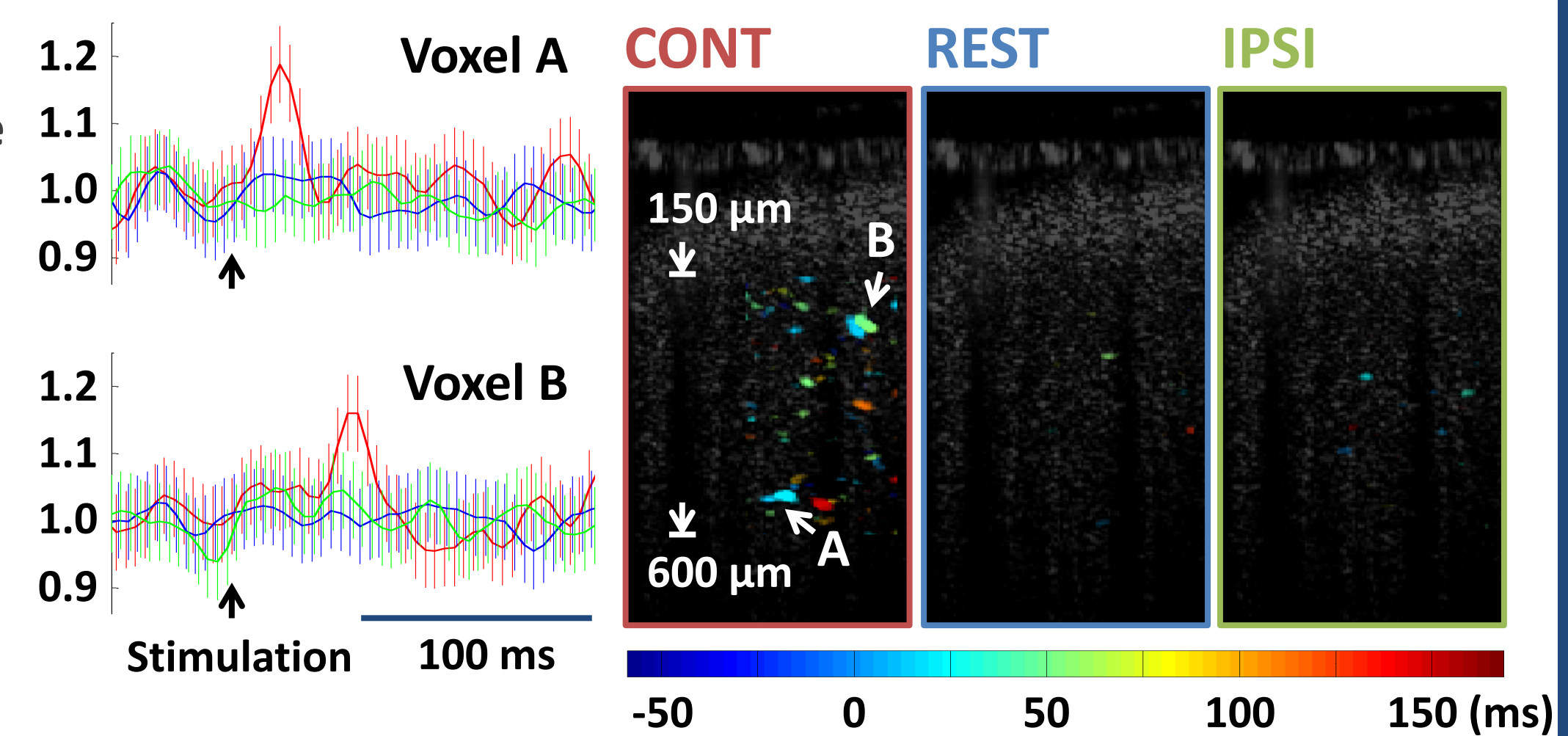
FUNCTIONAL IMAGING – NEURAL ACTIVITY

Depth-resolved Imaging of tOR (R_D/R_X)



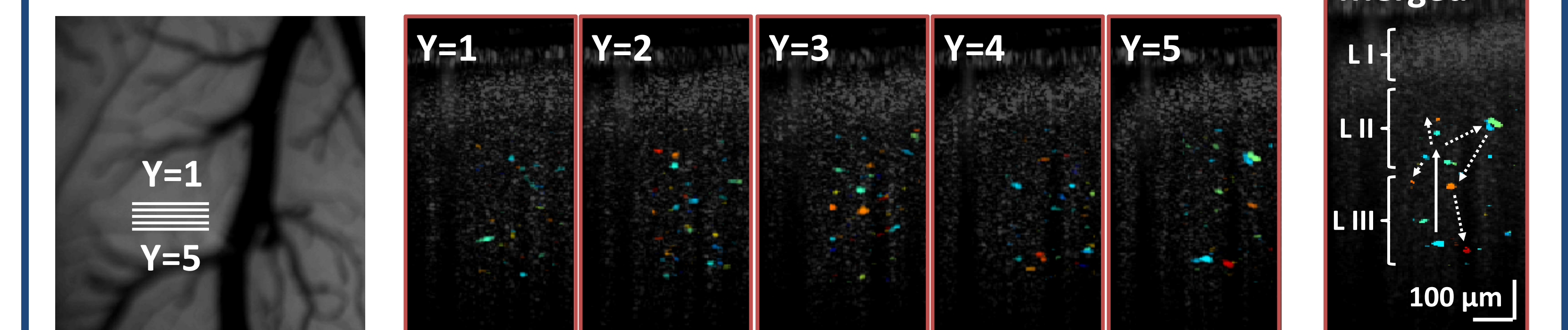
Reflectivity displacement (RD) RD was normalized by the variance of stochastic component (R_X).

The sequential images illustrate dynamic imaging of tOR in the case of contralateral stimulation (averaged over $n=30$ and spatio-temporal Gaussian kernel). Green spots indicate RD values larger than 1.1.



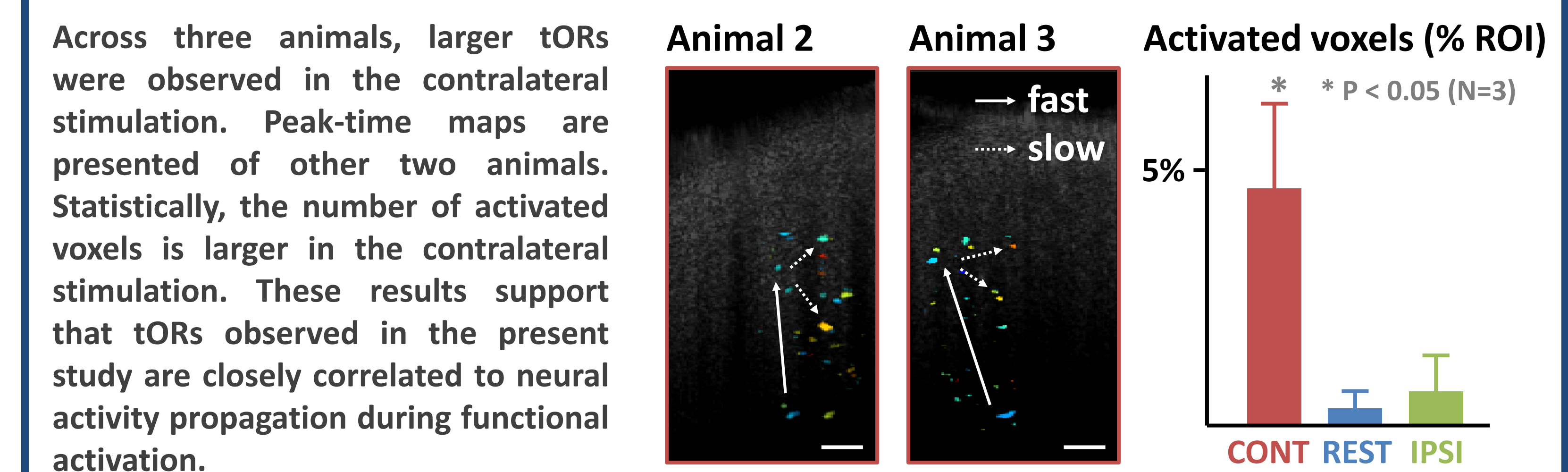
Time courses at two selected voxels are shown for three cases: contralateral stimulation (red), resting period (blue), and ipsilateral stimulation (green). Time of the maximum RD is color-coded at every voxel. Maps of this peak-time are presented for the three cases. In the peak-time map, the opacity is proportional to RD values ranging from 1.12 to 1.15. As can be seen in the three maps, Peak time at each voxel is color-coded in the map.

Preliminary Three-dimensional Imaging



Identical stimulation and imaging were performed at five neighboring cross sections (20- μm step). Peak-time maps from each Y position were merged with maximum projection. Preliminary functional connectivity maps are introduced for visual guidance (white arrow). The line arrow indicates a fast propagation with <10 ms time gap, while the dotted arrow indicates a slow propagation with >10 ms time difference.

Validation across Animals



CONCLUSION

This study uses SD-OCT for label-free imaging of tissue dynamics in the cortex, especially the hemodynamic response and neural activity propagation during functional activation. A novel analysis method, speckle decomposition technique, is proposed and validated. These results demonstrate the feasibility of noninvasive, label-free, and three-dimensional dynamic imaging of cortical activation with μm and ms resolution.

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