Full-field imaging of cerebral blood flow in freely moving animals

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A new miniature imager captures full-field cerebral blood flow in ambulating rats based on high-resolution laser speckle contrast analysis.

Functional and structural imaging of the cerebral neurovascular system has proven to be an important tool in neuroscience research. For example, functional magnetic resonance imaging and positron emission tomography provide 3D information about brain blood volume, which changes in response to metabolic alterations. But spatiotemporal resolution is limited, and subjects must be constrained or under anesthesia. In many areas of neuroscience investigation, neurovascular responses in the awake state are of great interest because anesthesia may affect the way neural circuits work.

In recent years, laser speckle imaging (LSI) based on laser speckle contrast analysis (LASCA) has been developed for monitoring cerebral blood flow (CBF). It has found application in biomedical research, e.g., hemodynamic response induced by tumor, retinal damage, or stroke, or peripheral electrical stimulation. Inspired by the miniature head-stage-based two-photon microscope and laser Doppler recording for freely moving animals, we developed a small head-mounted LSI system for cerebral vascular imaging. Two major challenges of such a device include integrating the image sensor, light source, micro-lens, and data acquisition chips into a wearable package that is sufficiently small and lightweight (e.g., ~20g), and removing motion artifacts when the animal (e.g., a rat) is moving without losing the data resolution.

The imaging system has two components: a high-resolution CMOS sensor (1024 × 1396 pixel resolution, 8-bit data precision, 35MHz pixel clock, 50fps frame rate, 10ms exposure time, 640 × 640 pixel area of interest) on a portable printed circuit board (3.6 × 3.6cm) that is used to record the speckle images from the cerebral cortex; and four collection lenses that serve together as an imaging lens system (3.44mm radius, 6.2mm focal length, 20mm minimum focus distance). A fiber bundle delivers the coherent laser light (780nm, collimated from a laser
diode). Figure 1 shows the entire imaging system mounted on a freely moving rat. Videos show a rat wearing a head-mounted LSI imager in an ambulatory state, and a rat undergoing treadmill training in an experiment related to rehabilitation following stroke.6,7

We implemented two techniques to ensure high-spatiotemporal-resolution imaging. The first is registered LASCA8 for correcting motion artifacts by overlaying speckle images. The second is a random process estimator to improve the signal-to-noise ratio of contrast images when using fewer frames.9

The imager provides high performance (161 pixels/mm resolution and <2% distortion), with each pixel corresponding to a 12.5×12.5μm cortical area that is sufficiently small for imaging tissue perfusion (i.e., blood flow at the capillary level). Figure 2 shows a typical contrast image obtained in a rat where the diameter of the smallest recognizable vessels was 50μm.

In summary, this miniature head-mounted LSI for full-field high-resolution imaging of CBF can be used in freely moving small animals, such as rats. The system offers the possibility to study the functional brain network of small conscious and ambulatory animals. As next steps, we plan to implement VLSI (very large scale integration) design to further reduce the size and weight of the imager for freely moving mice. We will also combine optical intrinsic signal imaging and LSI to enable our next-generation imager to simultaneously monitor CBF, blood volume, and (de)oxyhemoglobin.

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References