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Editorial

In vivo Optical Neuroimaging: Technological Development to Fit the Needs for Studying Drug-Induced Brain Functional Changes

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Licit and illicit drug use places a large burden on the nation's healthcare systems and economy, costing billions of dollars each year. According to the 2011 National Household Survey, about 22.5 million Americans, aged 12 or older, or about 8.7% of the population, were current users of illicit drugs [1]. Drug use often begins during adolescence and its effects are more long-lasting and resistant to treatment than when initiation occurs during adulthood. Additionally, drug use is a risky behavior that occurs with high frequency among those with HIV/AIDS and often co-exists with other psychiatric disorders and contributes to mortality from accidents particularly among young people. Substance abuse and addiction are serious national health issues [2] and understanding their neurobiological mechanisms and neurovascular complication would enable us to develop strategies for effective treatment and prevention.

Substance abuse results in profound and wide-range changes in brain chemistry, morphology, physiology and function. Although researchers have made enormous strides in identifying the receptors for each major drugs of abuse and in clarifying the neural circuitry involved in addictive processes, the physiological and functional changes in the brain during drug use or after chronic exposure to substances of abuse are not fully understood. For example, one of the most serious medical risks of cocaine abuse is stroke due to the drug's disruption of blood flow in the brain. About 25% to 60% of cocaine-induced strokes can be attributed to cerebral vasospasm and ischemia [3-6]. The resultant neurologic deficits can range from mild and transient (e.g., facial paralysis) to severe with permanent disability (e.g., tetraplegia [7]). Brain imaging studies have documented marked decreases in cerebral blood flow (CBF) and blood volume (CBV) in cocaine abusers [8]. However, the mechanisms underlying cocaine-induced CBF reduction, cerebral vasospasm and ischemia are poorly understood. The possibilities include: 1) direct vasoconstrictive effects elicited via cocaine-induced intracellular calcium ($[Ca^{2+}]_i$) increase in vascular smooth muscle cells [9], 2) indirect vasoconstriction secondary to the release of sympathomimetic amines, 3) a local anesthetic action secondary to blockade of ion channels, or 4) an indirect effect of reduced neural activity and metabolic demand [8]. Therefore, separation of neuronal from vascular effects of cocaine is crucial to understanding the mechanisms that lead to neurovascular toxicity in cocaine abusers.

The ability to distinguish the neuronal effects from vascular effects of cocaine remains technical challenge for Biotechnical and Biomedical Engineering communities because the technological requirements necessary for this endeavor include:

a). **A large field of view** to provide three-dimensional (3D) quantitative imaging of the CBF network;

b). **High temporal resolution** to enable capturing real-time responses of brain during drug intoxication;

c). **High spatial resolution** to permit separation of vascular compartments (e.g., artery, vein and capillary) and image their vascular hemodynamic changes without fluorescence labeling;

d). **Multimodality simultaneous imaging** to enable quantification of hemodynamics, tissue oxygenation and cellular activities induced by cocaine.

e). **Imaging deep underneath the cortical surface** to access subcortical brain areas involved in addictive process of the drug (e.g., striatum, nucleus accumbens) and to image the functional changes in specific neuronal populations (i.e., neurons expressing D1 or D2 receptors) *in vivo* with cellular resolution.

Noninvasive and high spatiotemporal-resolution imaging of cerebral hemodynamic and neuronal effects in response to drug challenges remains a major challenge in neuroimaging. Although conventional neuroimaging tools such as PET and functional MRI (fMRI) have greatly advanced our understanding of the pharmacological and physiological effects of cocaine [8,10], the

spatial resolution of these imaging techniques (e.g., >1mm) is insufficient to resolve individual vascular compartments or cells [11,12]. While optical microscopy (e.g., multi-photon microscopy) has shown some promise for visualizing capillary vasculature and cellular details of the cerebral cortex of rodents *in vivo*, its field of view (FOV) is too small and the image depth is limited (e.g., ~300μm) [13]. Other imaging approaches using intrinsic hemoglobin contrast such as laminar optical tomography (LOT) [14] and laser speckle imaging (LSI) [15] have been reported to map the brain's hemodynamic activity with improved spatial resolution; however, LOT is unable to resolve individual vessels and LSI only measures 'relative' changes in CBF.

We recently developed a dual-wavelength laser speckle imaging system (DWLSI). While LSI permits 2D imaging of CBF at high spatiotemporal resolutions (e.g., 30μm, 10Hz), it is based on *en face* imaging and only measures the relative flow indices rather than the absolute flow rates. Doppler optical coherence tomography (OCT) is an emerging optical technique that enables quantitative 3D imaging of the vascular CBF network (absolute flow rate detection) at high spatial resolution (10μm) over a large FOV in the cerebral cortex of the rodent's brain. Recent advances in digital-frequency-ramping OCT (DFR-OCT) have dramatically improved the sensitivity of Doppler OCT for detection of cerebral capillary flow (e.g., ~10μm, 0.16mm/s) [16] and the frame rate needed to render 3D imaging of the vascular CBF network within 8s/volume [17]; however, post image processing is needed because of intensive computation required to reconstruct quantitative 3D DFR-OCT flow images. By co-registering with DFR-OCT, it is found that LSI can be calibrated [18] to allow for high-resolution absolute quantitative imaging of transient CBF changes in real time (e.g., 10-29Hz). Moreover, DW-LSI can measure changes in both [HbO_2] and [HbR], thus enabling determination of the change in total hemoglobin concentration (i.e., Δ[HbT] or ΔCBV) in both CBFs and tissue perfusion (i.e., irresolvable capillary flows). Therefore, we developed a multimodality neuroimaging platform that combines DFR-OCT, DW-LSI and fluorescence to allow for simultaneous characterization of the local changes in cerebrovascular hemodynamics (CBF, CBV), hemoglobin oxygenation (HbO_2) and intracellular calcium ($[Ca^{2+}]_i$) fluorescence (to reflect cellular activity) for monitoring the effects of cocaine on the brain [17]. Such a multimodality imaging technique (OFI) provides several uniquely important merits, including: 1) large FOV (~35mm^2), 2) high spatiotemporal resolutions (~30μm, ~10Hz), 3) quantitative 3D imaging of the CBF network by co-registering with DFR-OCT, 4) label-free imaging of hemodynamic changes, 5) separation of vascular compartments between arterial and venous vessels and monitoring of cortical brain metabolic changes, 6) simultaneous imaging and thus separation of cellular (neuronal) from vascular responses, and 7) the ability to separately measure CBF in the layers of the cerebral cortex in the rodent brain. These imaging innovations have been further advanced in combination with microprobes to form micro-OFI (μOFI) that allows quantification of drug effects on subcortical brain [19]. Following on these novel advancements leads to our development of ultrahigh-resolution ODT (μODT) that enables 3D microangiography and quantitative imaging of capillary CBF networks [20]. These optical strategies have been used to investigate the effects of cocaine on brain physiology. These innovative strategies are a major thrust of our ongoing research and will facilitate the studies of brain functional changes induced by addictive substance such as cocaine to provide new insights into neurobiological effects of cocaine on the brain.

It should be noted that optical imaging techniques including OFI presented above are somehow invasive as a tradeoff for high resolution and sensitivity. However, many pioneering studies have demonstrated that optical imaging could be performed in awake animals. For instance, Grinvald and colleagues [21] imaged ocular dominance maps in an awake, untrained monkey. Ocular dominance, orientation and color maps were obtained in an awake, fixated monkey by Vnek et al. [22]. Optical imaging has also been applied to demonstrate the organization of the parietal and prefrontal cortex [23,24], and a spatial topographic map for working memory in monkeys performing a delay-match-to-sample task [24]. These and other studies by using miniaturized microscopic probes indicate that OFI could have great potential as a useful tool to study brain function in behaving animals in the near future.

In summary, *in vivo* optical imaging tools that will enable to measure cellular and vascular aspects of brain function will provide new insights into the neuropathological process of brain disease (i.e., addiction, neurodegeneration, traumatic brain injury), when used synergistically with other neuroimage modalities such as PET, fMRI and electrophysiology. They will also be valuable for evaluating the efficacy of novel pharmacotherapies and thus facilitate translational work. We believe these approaches can readily be translated to a range of other biomedical challenges, including insights into etiology of other diseases of the brain. Our research was supported in part by National Institute of Health (NIH) grants K25-DA021200 (CD), 1RC1DA028534 (CD, YP), R21DA032228 (YP, CD) and R01DA029718 (CD, YP) and by the NIH intramural programs (NDV).

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