Transcranial recording of stimulated neuronal activity *in vivo* using photoacoustic voltage-sensitive dye imaging

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Abstract: Non-invasive monitoring of electrophysiological brain activities in real-time has been demanded in neuroimaging field, which can quantify the functional neuronal depolarization events without any need for invasive craniotomy. Here we present *in vivo* proof-of-concept results for non-invasive sensing of neuronal activities in rat brain by using transcranial photoacoustic imaging of fluorescence quenching-based near-infrared voltage-sensitive dye (VSD) delivered through blood-brain barrier (BBB) using pharmacological modulation of Adenosine receptor signaling. Using the frequency-domain signal analysis on temporal photoacoustic sequence obtained at near-infrared isosbestic point of oxy- and deoxy-hemoglobin (i.e., 790 nm), the amount and firing frequency of brain activity have non-invasively quantified from those of control groups without VSD administration and/or stimulated brain activity. These studies demonstrate that photoacoustic imaging of fluorescence quenching-based VSD is a powerful tool for recording deep brain activities of rat brain without any fatal craniotomy.

Summary: Non-invasive monitoring of electrophysiological brain activities in real-time has been demanded in neuroimaging field. Here we present *in vivo* proof-of-concept results for non-invasive sensing of neuronal activities in rat brain by using transcranial photoacoustic imaging of near-infrared voltage-sensitive dye (VSD). Using the frequency-domain signal analysis on temporal photoacoustic sequence, the amount and firing frequency of brain activity have successfully quantified *in vivo*. These studies demonstrate that photoacoustic imaging of fluorescence quenching-based VSD is a powerful tool for recording deep brain activities of rat brain without any fatal craniotomy.