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Contrast Mechanisms

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Off-Target Effects of DREADD Actuators Result in Attenuation of BOLD Responses to Optogenetic Stimulation

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Designer receptors exclusively activated by designer drugs (DREADDs) provide a reversible method to excite or inhibit targeted neuronal subtypes and are widely applied in animal fMRI studies to examine functional connectivity. Although DREADD actuators are generally considered inert in neurophysiological and behavioral assays, their potential non-neuronal effects on hemodynamic signals are less well understood. In this study, we investigated whether three actuators—CNO, JHU37160, and DCZ—alter optogenetically evoked BOLD responses and hypoxia-induced CBV changes in mice lacking DREADD receptors.

We used transgenic mice expressing ChR2 in excitatory neurons (n = 12, JAX #007612). Each mouse was implanted with a fiber-optic cannula above the right primary motor cortex (M1). MRI scans were performed on a 15.2T Bruker Biospec system (TR/TE = 1000/11.7 ms, 0.156 × 0.156 mm, 20 slices at 0.5 mm) under anesthesia with continuous dexmedetomidine infusion (0.05 mg/kg/h) and 0.3% isoflurane. The block design included an initial 5-min resting-state scan, followed by three trials of optogenetic M1 stimulation (3 mW, 20 Hz, 20% duty cycle, 20 s stimulation, 60 s recovery, repeated twice per trial), and six trials of hypoxia-induced BOLD-DSC (100% N_2 for 5 s, 60 s recovery). Each block lasted ~30 min and was repeated four times. After the first block, mice received one of the actuators: CNO (1 mg/kg), JHU37160 (0.5 mg/kg), or DCZ (0.1 mg/kg).
Baseline optogenetic stimulation of M1 produced widespread activation in both cortical and subcortical regions. Following drug administration, we observed attenuation of both positive and negative BOLD responses. To quantify this effect, we analyzed voxel counts showing significant responses over time. CNO produced clear attenuation beginning ~35 min post-injection. JHU37160 induced rapid attenuation within 5 min, peaking at ~35 min. DCZ produced a similar effect to JHU37160, though the attenuation subsided by ~65 min.
The effects on hypoxia-induced CBV changes mirrored the attenuation of optogenetically evoked BOLD responses. Specifically, rCBV increases during hypoxia coincided with the time window of BOLD response suppression, suggesting that vascular dilation may underlie the observed changes.

In summary, we demonstrate that three different DREADD actuators can alter BOLD and CBV signals in the absence of DREADD receptors. These off-target effects were consistent with the expected arrival time to the brain. Our findings indicate that the interpretation of DREADD-fMRI data must carefully account for potential drug-induced hemodynamic changes independent of neural activity.

Keywords: *Optogenetic fMRI, DREADD, BOLD response, Cerebral blood volume (CBV)*