

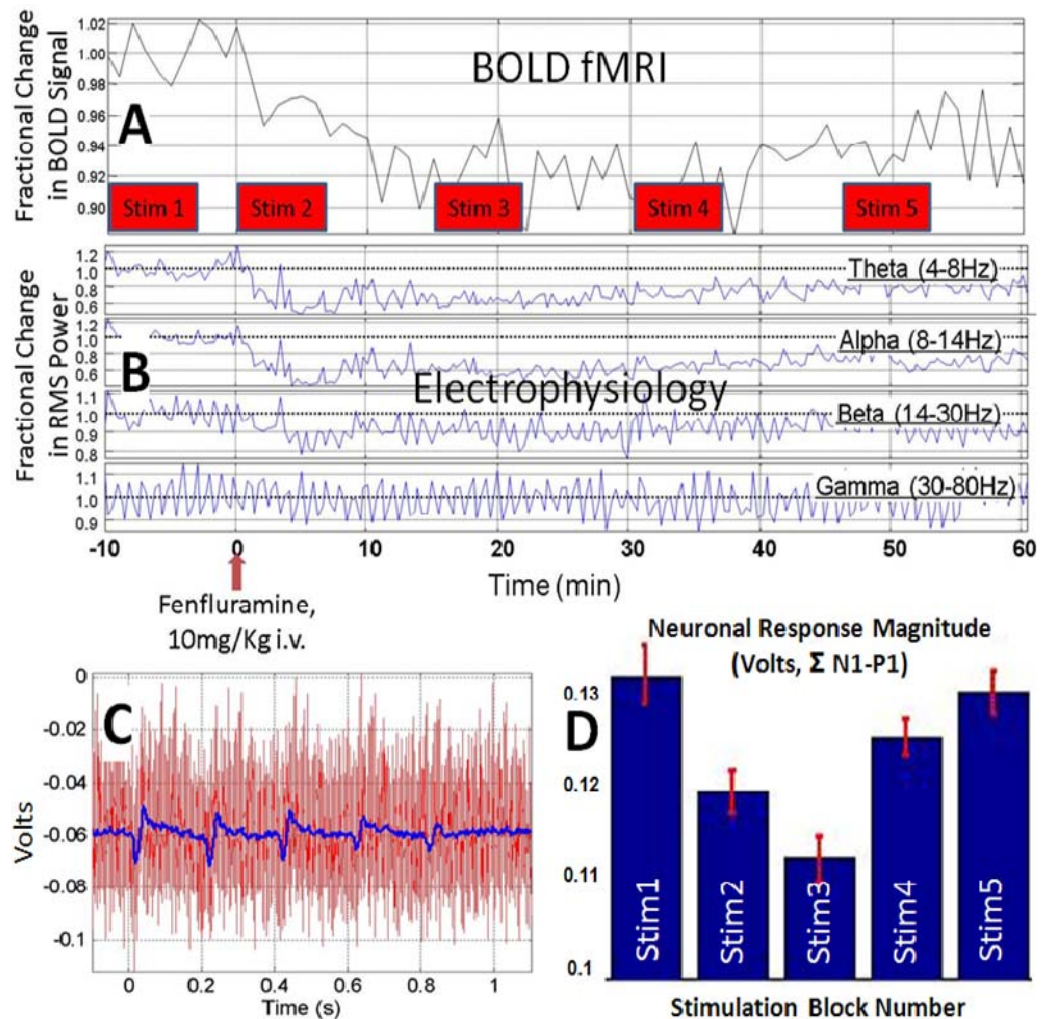
Concurrent pharmacological MRI and electrophysiology to investigate neuropharmacological modulation of brain function in the rat

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Introduction: Functional brain imaging methods which exploit the neurovascular coupling of neuronal activity to changes in hemodynamics are increasingly applied to study the functional effects of neuropharmacological agents in both human and animal subjects. A problem is that neuroimaging signals such as the blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal may be subject to multiple neuronal, neurovascular, hemodynamic and systemic effects of the drug under investigation. To address this, our understanding of the neurophysiological basis of functional imaging signals must be expanded to include the effects of altered neurotransmitter function (e.g. by experiment, clinical trial or disease) and differences across neuropharmacologically diverse cortical and subcortical structures. An effective approach for establishing relationships between fMRI responses and underlying neuronal activity is one in which both of these signals are measured concurrently. Achieving this within the MR environment is difficult due to distortion of electrophysiological signals by rapidly changing magnetic gradient fields. Here, we report the development of methodology for concurrent acquisition of fMRI and electrophysiological measures of neuronal activity in the rat. We use this method to investigate the effects of the serotonin releasing agent, fenfluramine, on both baselines and stimulus evoked responses.

Methods: Animals were anesthetized with isoflurane, tracheotomized for artificial ventilation and cannulated for administration of drugs and monitoring of physiological parameters. Electrodes were constructed from carbon fibre bundles (diameter ~50microns) and inserted into the hindpaw sensorimotor cortex. Stimulating electrodes were inserted into the contralateral hindpaw. Imaging was performed on a 7-Tesla horizontal bore magnet. Anatomical scans to cover the whole brain were acquired using a T2-weighted fast spin-echo sequence (field of view 30X30mm, matrix size 128X128, slice thickness 0.5mm). Functional data were acquired using T2*-weighted multi-echo gradient-echo sequences (effective TE 12ms, field of view 30 X 30 mm, matrix size 128 X 64, slice thickness 0.5mm). Fenfluramine (10mg/Kg) was injected intravenously after a period of baseline data acquisition. Analysis procedures to remove the MR artefacts from the data included an adaptive template-based artifact removal procedure and band-pass filtering.



Results and Conclusions: We demonstrate that electrophysiological measures of both baseline and stimulation-evoked neuronal activity can be obtained concurrently with fMRI data acquisition. Fenfluramine administration produced simultaneous decreases in the BOLD fMRI signal (A) and in EEG power fluctuations (B). Neuronal responses to hindpaw stimulation could be easily extracted from the data following processing to remove MR gradient artifacts (C: red - before processing, blue - after processing). Neuronal responses were also transiently attenuated by fenfluramine administration (D). These procedures will be used to investigate the effects of neuropharmacological manipulation of neurotransmitter function on the relationship between neuronal activity and fMRI responses. Methods for conducting experiments in awake animals are also being developed.