

Opto-fMRI of Monoaminergic Systems and Psychotropic Drugs

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Introduction

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Monoaminergic systems are ensembles of neurons defined by the primary production of monoamine neurotransmitters (most prominently serotonin, dopamine, and noradrenaline).

- ▶ Their wide-spread projections have implicated them in numerous neuropsychiatric disorders (e.g. depression, anxiety, addiction, and schizophrenia).
- ▶ Their relevance to the control of neuronal function has made them targets of many therapeutic drugs (e.g. monoamine reuptake inhibitors) and drugs of abuse (e.g. amphetamines).
- ▶ A high degree of evolutionary conservation makes them excellent candidates for translational research in rodents.

The current project aims to establish opto-fMRI as an assay for monoaminergic systems. This assay will help elucidate the functional mechanisms of psychotropic drugs, and facilitate the establishment of functional connectivity and inter-connectivity models for these most pervasive neuronal systems.

Figure 1: Serotonergic (green), dopaminergic (red), and noradrenergic (blue) nuclei and significant projections^[1]

Figure 2: Ascending serotonergic projections alone innervate the majority of cortical and subcortical areas^[2]

Methods

Optogenetic stimulation requires a number of preliminary procedures, including the breeding of genetically modified mice, the targeted infusion of a light-gated protein (ChR2) expressing viral vector, and the targeted implant of a durable optic fiber ferrule.

Figure 5: (a) Optic fiber implant targeted at the serotonergic dorsal raphe (DR); histological validation of the ChR2 construct expression: (b) localized to the DR and (c) colocalized with serotonin. Data from Saab and colleagues, unpublished.

For robust genotyping we have designed 2 multiplex-compatible primer pairs for the Cre recombinase (transgene construct) and GAPDH (positive control). These are listed below, alongside a genotyping assay featuring 3 controls (water, known transgene, and known wildtype - on the first, second-to-last and last non-ladder lanes respectively):

Direction	Target Construct	
	Cre	GAPDH
fw	ACCAGCCAGCTATCAACTCG	CTCCATTTCCTCTCTCC
rv	TTGCCCTGTTTCACTATCC	GAGACCTGAATGCTGCTTC

To facilitate multimodal and exploratory data analysis, LabbookDB - a relational database structure - was developed to replace the common lab book and integrate metadata directly with analysis tools. In order to facilitate rapid, cheap, and flexible access to the high computing power needed for exploratory fMRI analysis, a cloud-computing GNU/Linux image, NeuroGentoo was created; and populated with a multitude of neuroimaging package atoms.

Figure 6: NeuroGentoo Logo; for the software repository see: github.com/TheChymera/neurogentoo

Figure 7: Generic DB logo (CC BY-NC-SA Barry Mieny); for the software package see: github.com/TheChymera/labbookdb

Chronic Serotonin Reuptake Inhibition

Selective Serotonin Reuptake Inhibitors (SSRI) are used in the treatment of depression, and have differing acute (e.g. stimulant and anxiogenic) and chronic (antidepressant and anxiolytic) effects - with the neuronal mechanism of the latter still being widely debated. Possible explanations include the down-regulation of either the serotonin transporter protein (SERT), and/or serotonergic autoreceptors (5-HT_{1A}). We are administering fluoxetine both chronically and acutely to a number of animals prepared for opto-fMRI; we present the timetable of the first cohort in figure 4.

Figure 3: Band-pass filtered pulse-train-resolved first-level design model, with pulse trains represented in cyan.

- ▶ Opto-fMRI can be used to analyze chronic SSRI effects on serotonergic neurotransmission - by modelling the effect of treatment on individual pulse trains, or the interaction effect of treatment and pulse train number on series of pulse trains (as seen in figure 3).
- ▶ The large-scale readout capacity of opto-fMRI can also detect whether there are regionally varying effects of chronic SSRI administration (and consequently allow a functional characterization of neuronal subpopulations of the dorsal raphe).

Figure 4: Animal cohort treatment and measurement timetable. Opto-fMRI scan dates are tinted turquoise. Treatment-free days are shaded light gray, chronic (i.p.) fluoxetine administration days medium gray, and acute (i.v.) fluoxetine administration days dark gray.

Acute Fluoxetine Effects

Preliminary results from the comparison of the first two measurement sessions (as seen in figure 4) indicate that the uncorrected response to optogenetic stimulation across all trains (depicted individually in figure 3) is stronger and more widespread immediately after acute fluoxetine administration than in the drug-naïve mouse. It is important to note that the results seen in figure 8 need further statistical elaboration.

Figure 8: Contrast for all stimulation train parameter estimates for the pre-drug-administration session (red) and the acute fluoxetine administration session (green). Note the considerably different scales.

References

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