Multivariate Guide to Magnetic Resonance Imaging and Optogenetic Control of the Mouse VTA

Horea-Ioan Ioanas[1] Bechara John Saab[2] Markus Rudin[1]
[1]Institute for Biomedical Engineering, ETH and University of Zurich
[2]Preclinical Laboratory for Translational Research into Affective Disorders, DPPP, Psychiatric Hospital, University of Zurich

Abstract — Ascending dopaminergic projections rooted in the Ventral Tegmental Area (VTA) are involved in numerous phenomena of great neuropsychological interest, including motivation, learning, and addiction. The study of dopaminergic signalling in humans is chiefly conducted via functional magnetic resonance imaging (fMRI), but is severely restricted in terms of molecular and cell biological interventions, as well as in terms of direct dopaminergic system control. Optogenetic fMRI (opto-fMRI) in the mouse model organism, affords the possibility of direct dopaminergic control, as well as whole-brain imaging using a modality identical to that used in human studies. As the dopaminergic system is also evolutionarily well-conserved, Work based upon this assay thus allows the identification of novel ways to modulate and categorize dopaminergic activity in both model animals and humans. In this article we explore the fundamentals of the assay and offer a comprehensive guide to best practices based on variation in multiple experimental parameters including implant positioning and stimulation protocols.

The Optimized Workflow

We perform statistical modelling with the Statsmodels [**?**] package, and incrementally hone in on variance sources, as the qualitative modelling of our variables precludes robust estimation of high-order interaction terms.

Reproducibility

The source code for this document and all data analysis shown herein (including registration and QC workflow execution) is published according to the RepSeP specifications [**?**]. The data analysis execution and document compilation has been tested repeatedly on numerous machines, and as such we attest that all figures and statistics presented can be reproduced based solely on the raw data, dependency list, and analysis scripts which we distribute.

Results

We note that the VTA mean t statistic is sensitive to the stimulation protocol (), but not to the depth () or the PA coordinates ().

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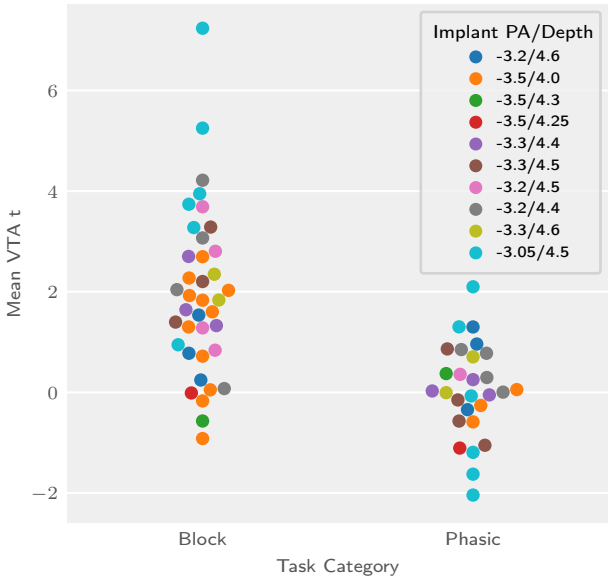
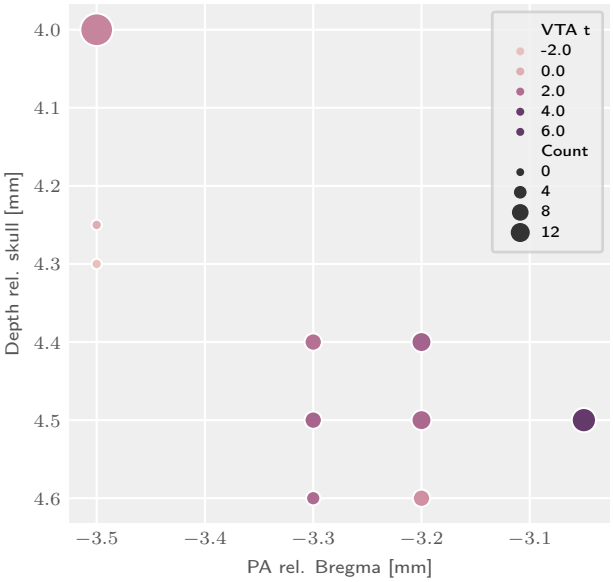
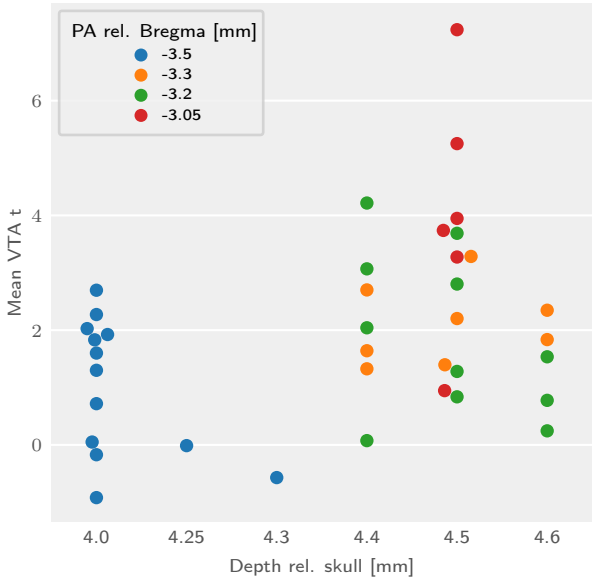


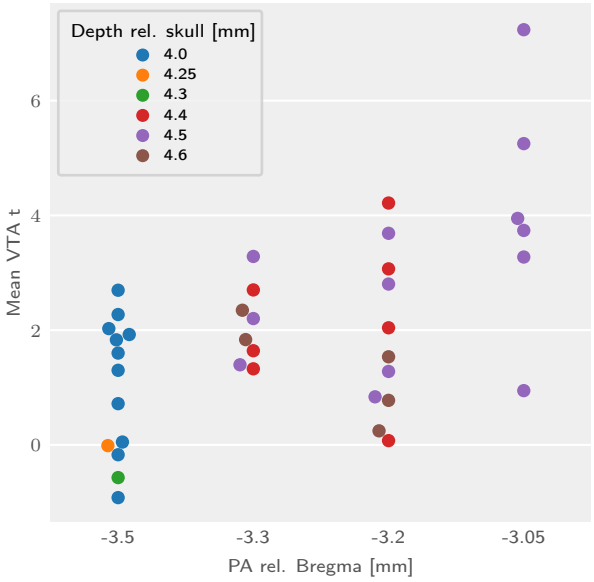
(a) Task group comparison for animals targeted with all implant coordinates.



(b) 2D implant coordinate comparison for block stimulation scans only.

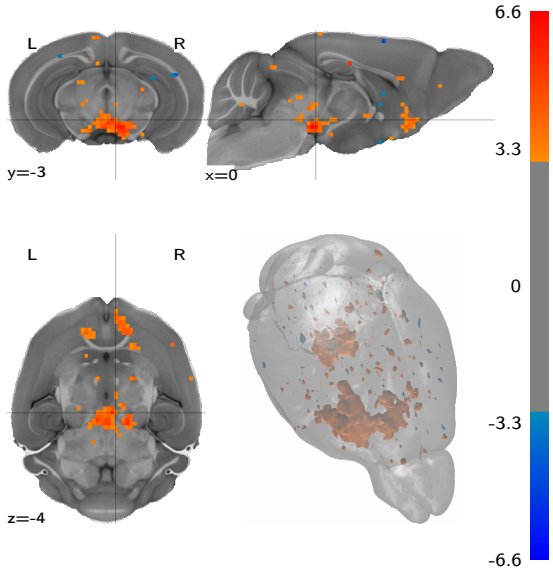


(c) Implant coordinate comparison for block stimulation scans only, sliced by depth.

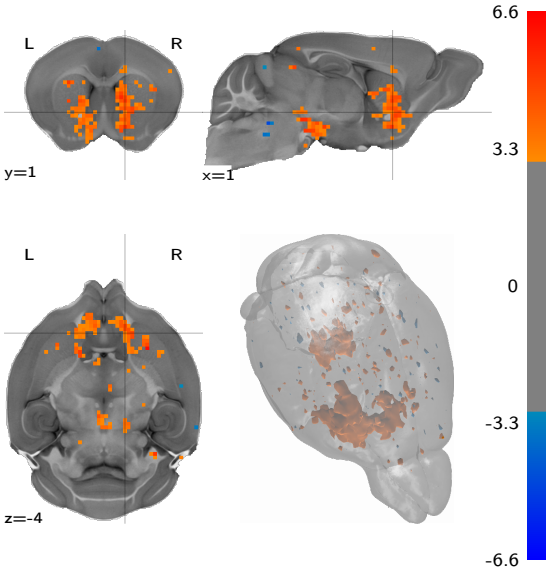


(d) Implant coordinate comparison for block stimulation scans only, sliced by PA coordinates.

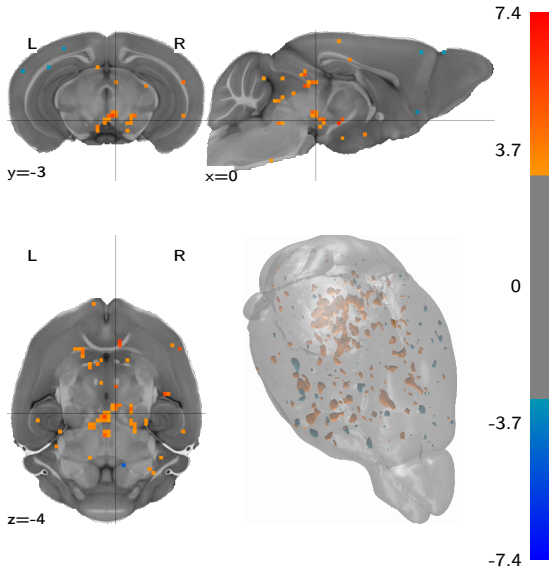
Figure 1: Multivariate (protocol and operative feature) comparisons of signal intensity in the VTA region of interest.



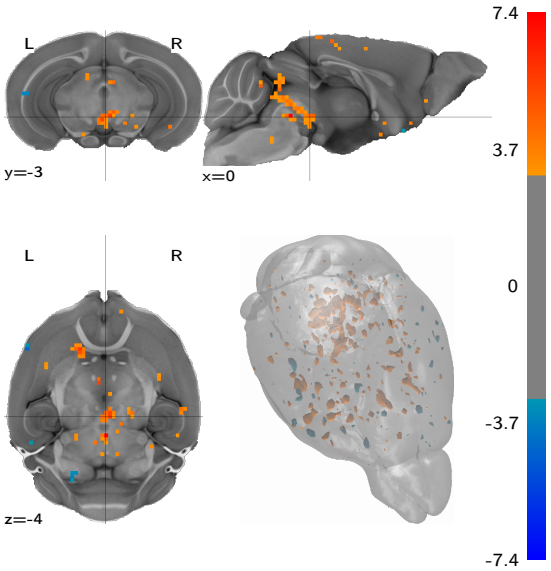
(a) Best coordinate group with slices centered on VTA.



(b) Best coordinate group centered on langest cluster.



(c) Remaining coordinate group centered on VTA.



(d) Remaining coordinate group centered on largest cluster.

Figure 2: Best coordinate group scans elicit activity in the Striatum and the Nucleus Accumbens, whereas remaining scans do not. Depicted are statistical maps (thresholded at $|\mathrm{t}| \geq 3$) of the second-level analysis for block stimulation protocols, comparing different subject groups segmented by implant coordinates — best coordinate group ($\mathrm{PA} \geq -3.3; \mathrm{IS} \geq -4.4$) and remaining scans. Slices are centered on VTA coordinates ($\mathrm{RAS} = 0.5 - 3.2 - 4.5$) and on the largest cluster, respectively.

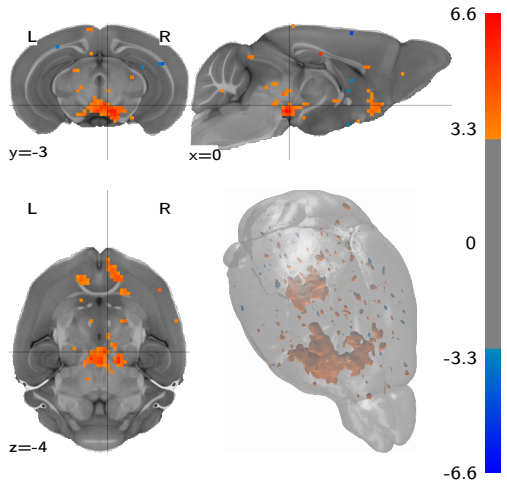
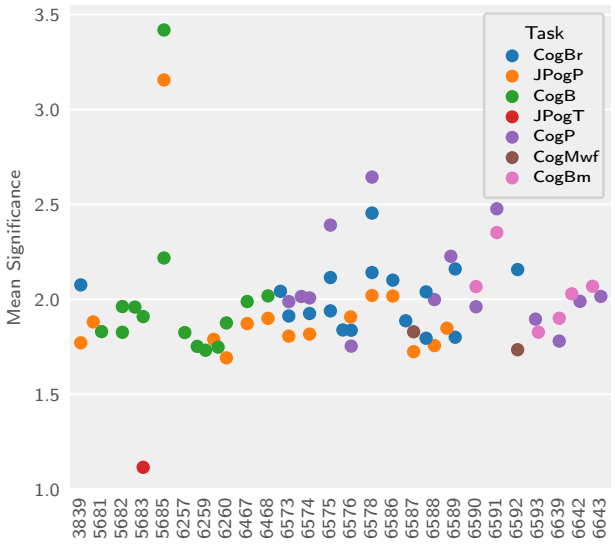
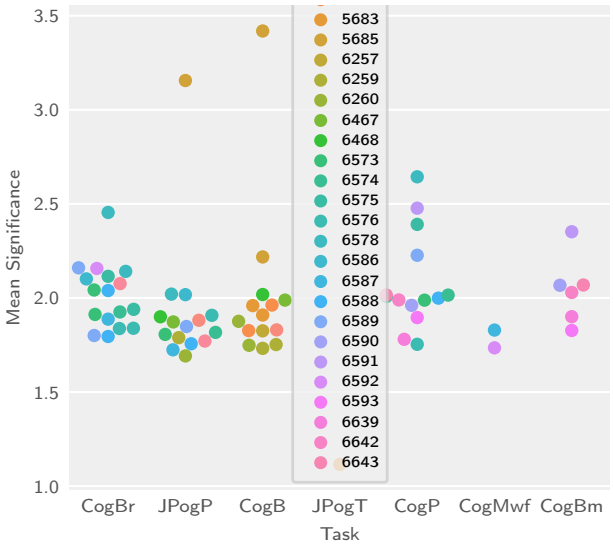


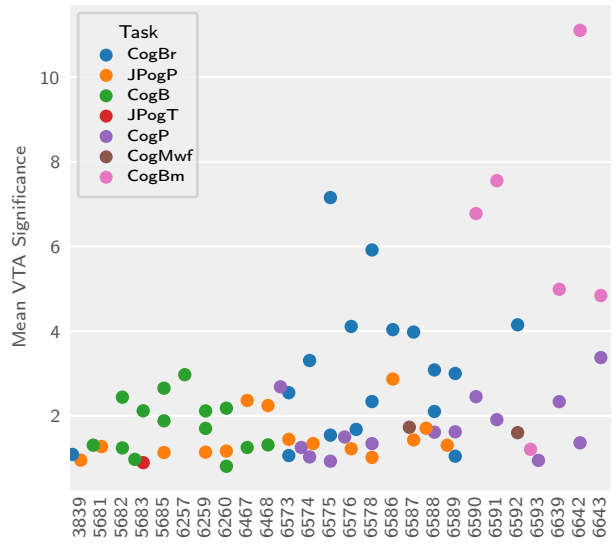
Figure 3: Task group comparison for animals targeted with all implant coordinates.



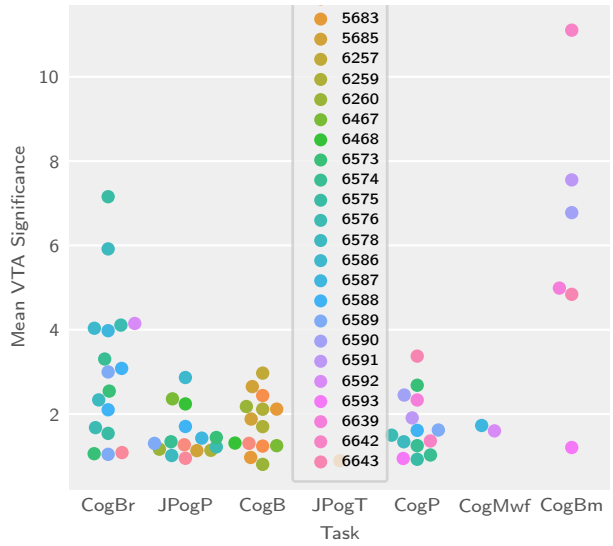
(a) Whole brain significance across subjects.



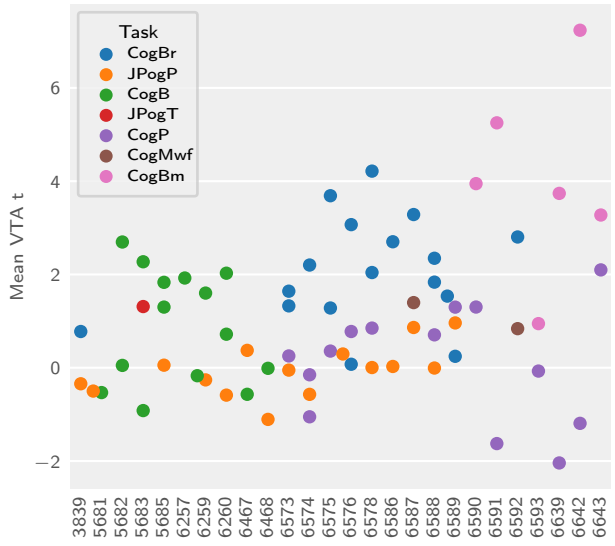
(b) Whole brain significance across stimulation protocols.



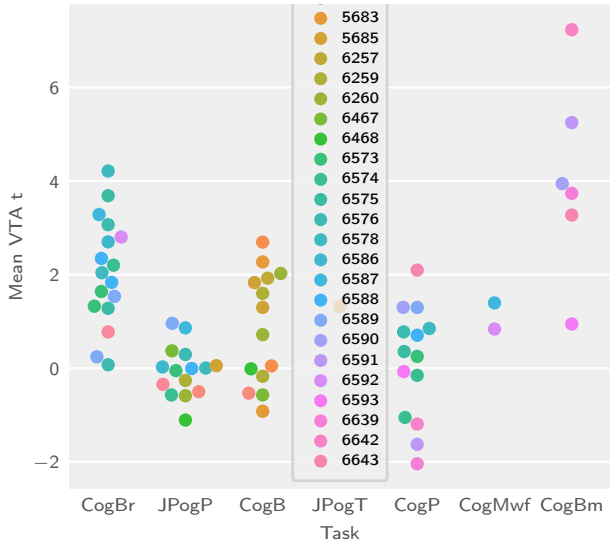
(c) VTA significance across subjects.



(d) VTA significance across stimulation protocols.



(e) VTA signal intensity across subjects.



(f) VTA signal intensity across stimulation protocols.

Figure 4: Multivariate (subject and stimulation protocol) comparisons of significance and signal intensity at the whole-brain level or restricted to the VTA region of interest.

Supplementary Materials

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