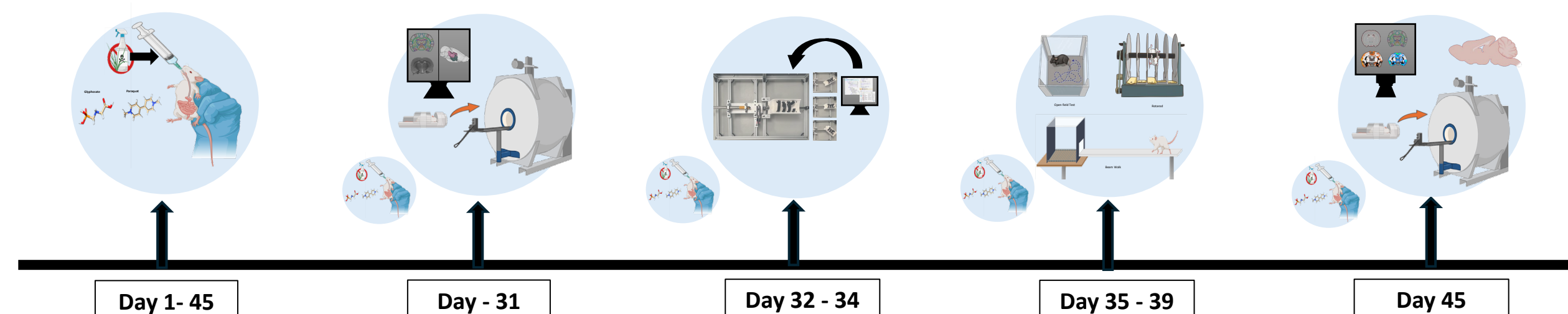


## Abstract

Parkinson's disease (PD) is a progressive neurological disorder that affects millions of individuals worldwide. Growing evidence has suggested that chronic exposure to environmental toxins, including commonly used herbicides such as paraquat and glyphosate, may contribute to PD pathogenesis through mechanisms involving oxidative stress. In parallel, mild traumatic brain injury (mTBI) has been associated with dopaminergic dysfunction and an increased risk of PD. We utilized a multimodal MRI approach to examine microstructural alterations, resting-state functional connectivity, and cerebrovascular reactivity. This integrated approach aimed to provide insight into central and peripheral mechanisms underlying Parkinson's disease.

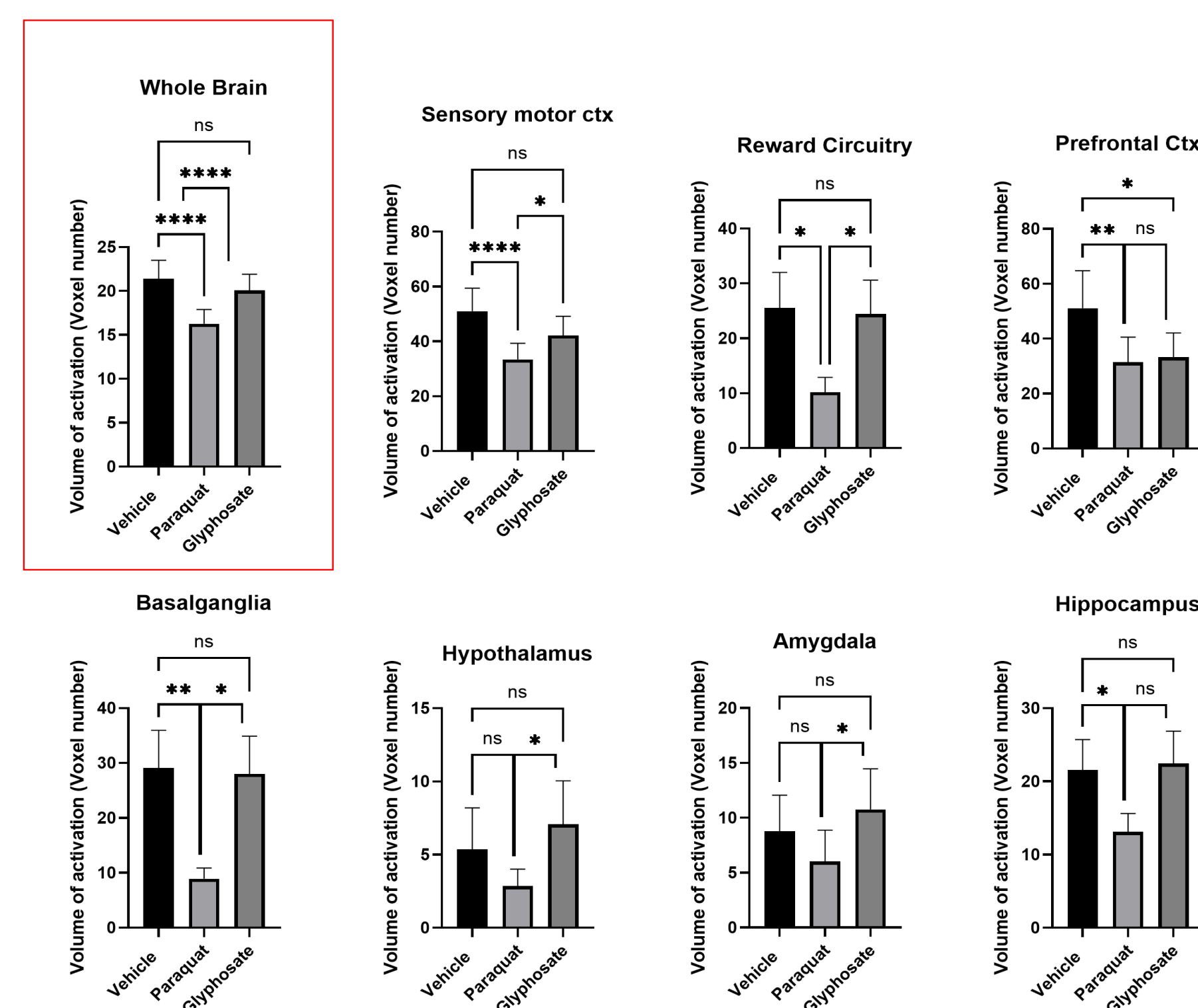
## Experimental Design

Adult Sprague-Dawley male ( $N=18$ ) and female ( $N=18$ ) rats staggered into 3 Cohorts vehicle, Paraquat, Glyphosate with each consists of 6 males and 6 females received daily oral dosage from Day 1–45. Diffusion-weighted imaging (DWI) was performed on Day 31. rmTBI was induced on Day 32–34. Behavioral assessment were occurred on Days 35–39. 2 weeks post-injury, fMRI, Functional connectivity and a follow up DWI was performed. finally, tissues were collected for further biomarker evaluation



Day 1 - 45	Day 31	Day 32 - 34	Day 35 - 39	Day 45
Oral gavaging treatment	Neuroimaging → Pre-injury	Repetitive mild traumatic brain injury (rmTBI)	Behavioral Assays	Neuroimaging Post-Injury
<ul style="list-style-type: none"> <li>Vehicle (saline) → every 3rd day</li> <li>Paraquat (10 mg/kg) → every 3rd day</li> <li>Glyphosate (75 mg/kg) → everyday</li> </ul>	<ul style="list-style-type: none"> <li>7.0 T Magnetic Resonance Imaging</li> <li>T2 weighted anatomy</li> <li>Diffusion Weighted Imaging (DWI)</li> </ul>	<ul style="list-style-type: none"> <li>Buprenorphine (subcutaneous) – Extended release (ER) 0.1 mg/kg</li> <li>Performed rmTBI using a controlled impactor (7.4 m/s) over 3 consecutive days.</li> </ul>	<ul style="list-style-type: none"> <li>Open Field Test (OFT)</li> <li>Novel Object Recognition (NOR)</li> <li>rotarod</li> <li>beam walk.</li> </ul>	<ul style="list-style-type: none"> <li>7.0 T MRI, T2-weighted anatomy</li> <li>Functional connectivity, fMRI (hypercapnic, benzaldehyde induced reward stimulus challenge)</li> <li>Diffusion Weighted Imaging (DWI)</li> <li>Post-Tissue collection → biomarker evaluation</li> </ul>

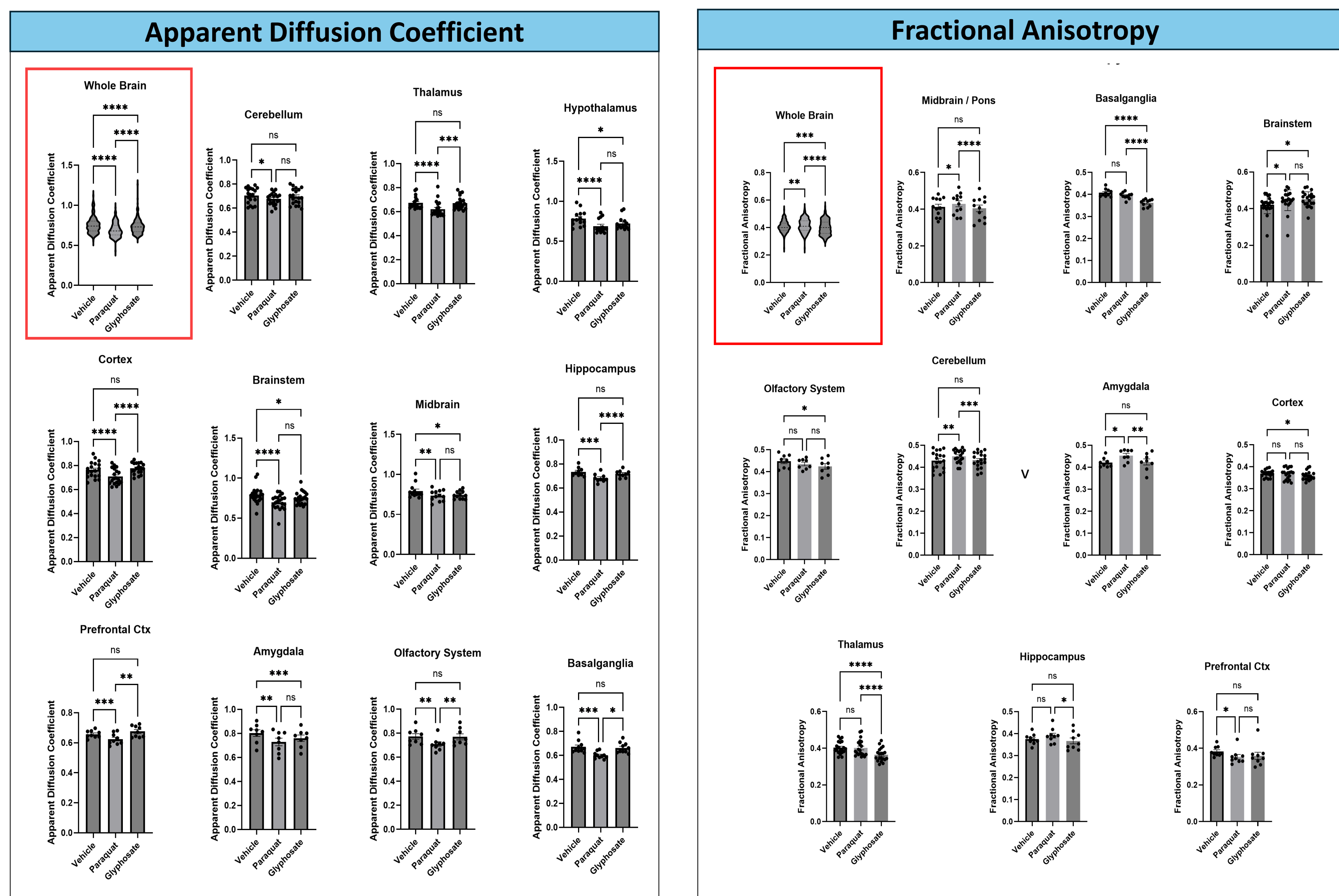
## Reward circuitry processing



The reduced positive BOLD responses to reward stimulation in the paraquat and glyphosate groups suggest impaired activation of dopaminergic reward circuits, potentially reflecting dysfunction within the nigrostriatal and mesolimbic pathways.

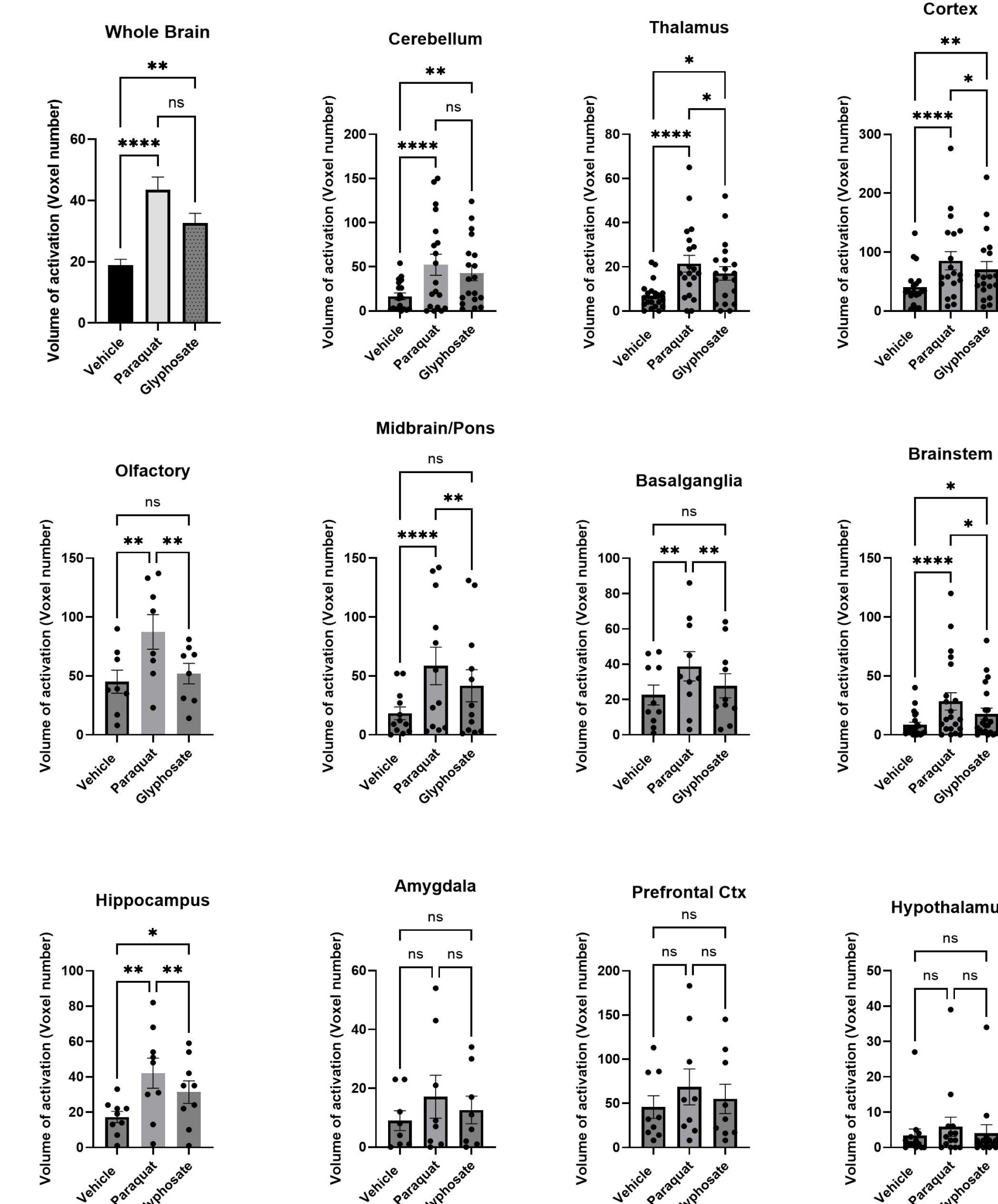
One-way ANOVA & Non parametric Friedman test \* $p<0.05$ , \*\*\*\* $p<0.0001$

## Diffusion Weighted Imaging (DWI) Analysis



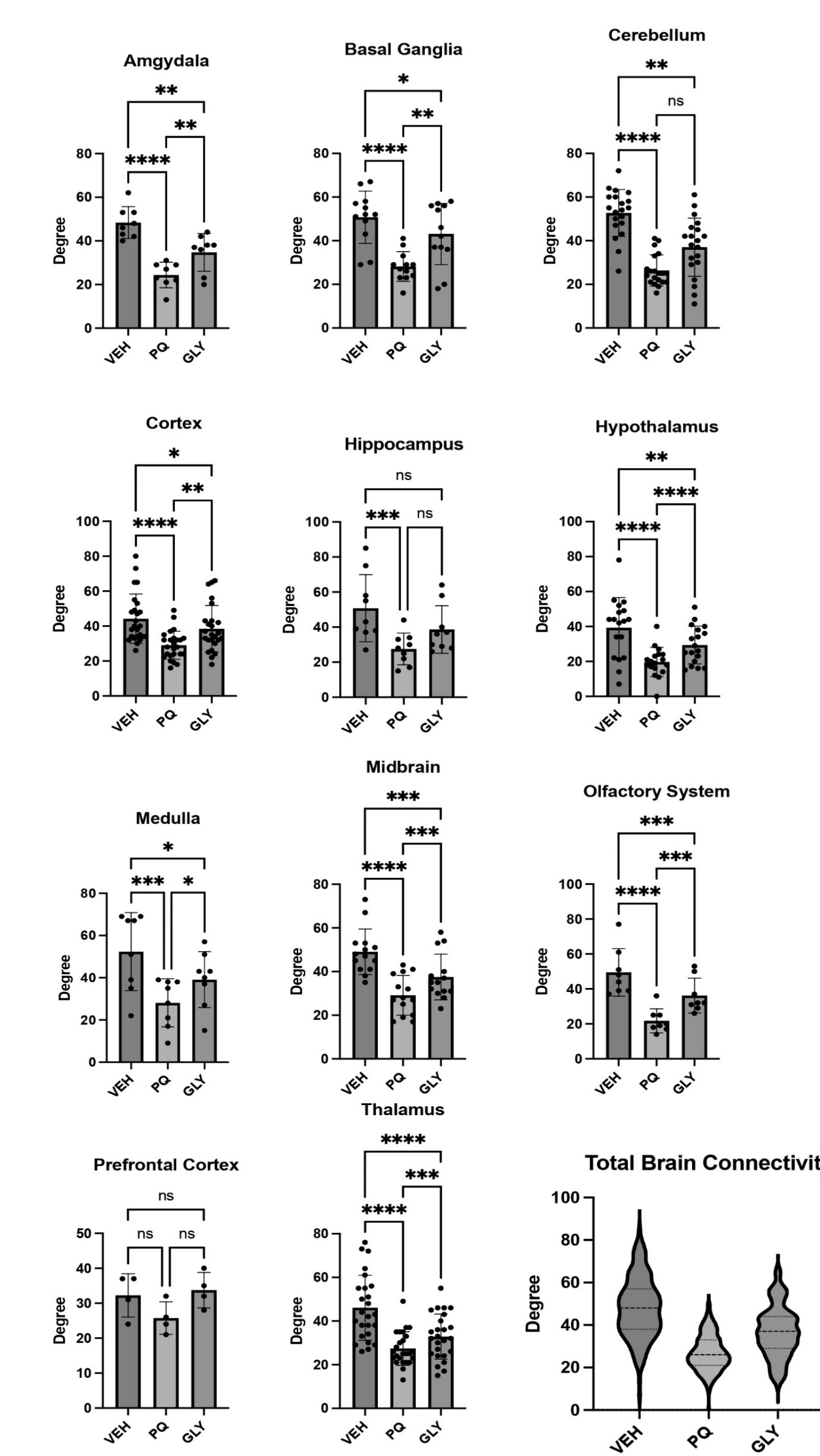
DWI revealed reduced ADC following chronic herbicide exposure and rmTBI, indicating restricted diffusion consistent with cytotoxic edema. Widespread reductions in FA suggest axonal injury and compromised white matter integrity, while localized increases in FA may reflect altered microstructural organization. Statistical differences between treatment groups (Vehicle, Paraquat, Glyphosate) were evaluated using **One-way ANOVA & Nonparametric Friedman test** \* $P<0.05$ , \*\*\*\* $p<0.0001$

## Herbicide exposure alters Neurovascular coupling

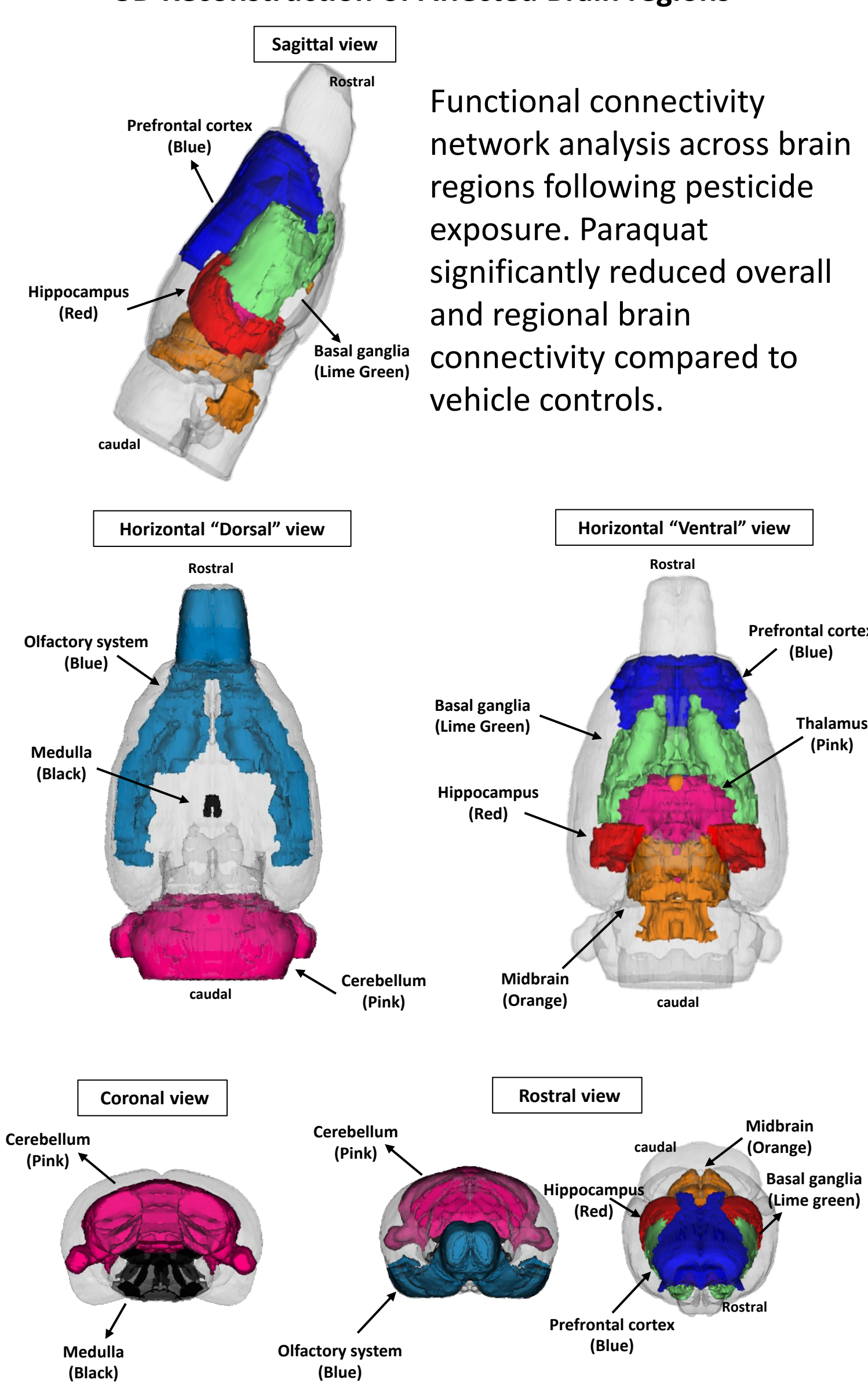


Herbicide exposure significantly enhanced hypercapnia-induced BOLD activation 45 days post-rmTBI. Paraquat elicited the largest increases in voxel-wise activation across multiple regions relative to vehicle controls, reflected by a greater number of positive BOLD voxels, suggesting altered cerebrovascular reactivity. **One-way ANOVA & Nonparametric Friedman test** \* $P<0.05$ , \*\*\*\* $p<0.0001$

## Functional Connectivity Network analysis

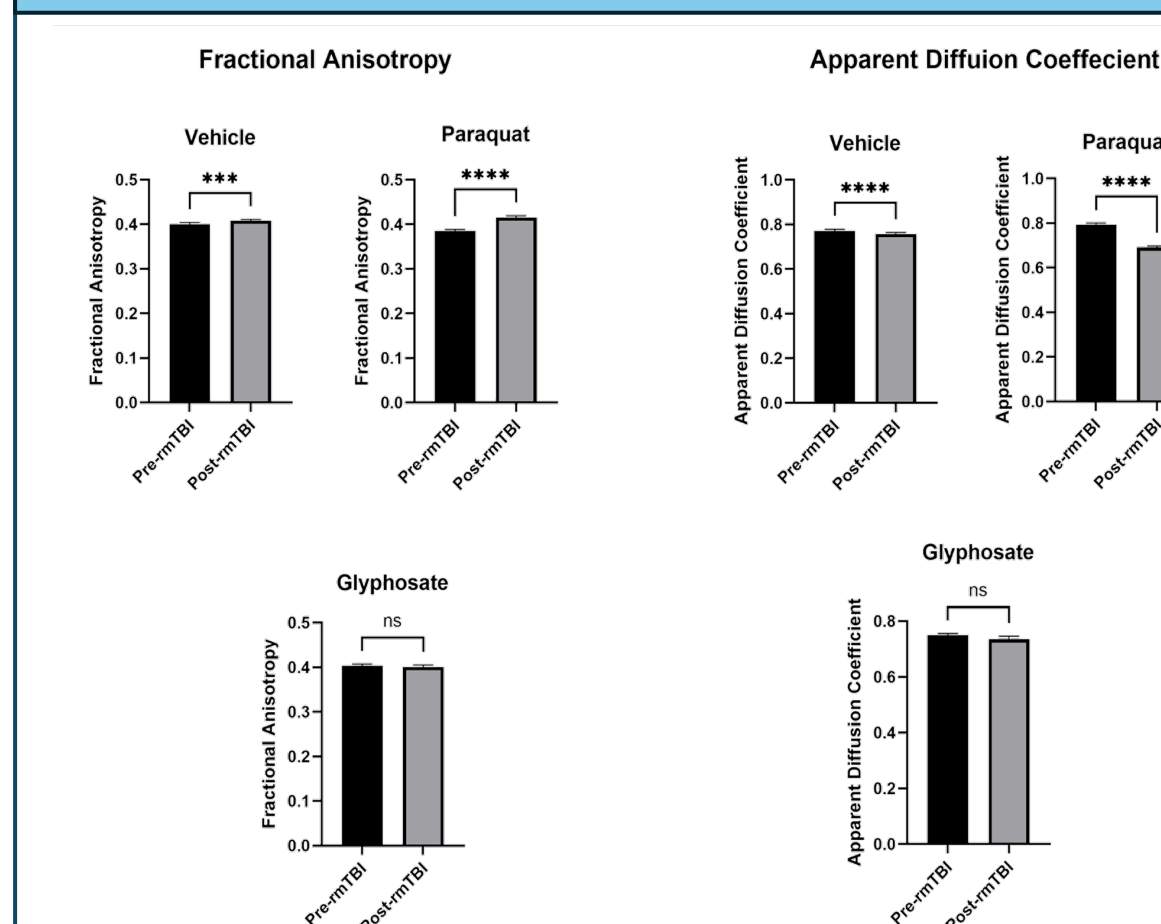


### 3D Reconstruction of Affected Brain regions



Functional connectivity network analysis across brain regions following pesticide exposure. Paraquat significantly reduced overall and regional brain connectivity compared to vehicle controls.

## Pre- vs. Post-rmTBI Comparative Analysis



The combination of elevated FA and reduced ADC following rmTBI suggests restricted diffusion with increased anisotropy, which may result from cellular swelling, reduced extracellular space, and early alterations in white matter organization. **One-way ANOVA & Nonparametric Friedman test** \* $P<0.05$ , \*\*\*\* $p<0.0001$

## Discussion

- Diffusion-weighted imaging (DWI) revealed reduced ADC and FA following herbicide exposure, suggesting restricted diffusion consistent with cytotoxic edema and potential axonal damage.
- Hypercapnia fMRI showed increased positive BOLD voxels, indicating altered cerebrovascular reactivity.
- Functional connectivity analysis demonstrated reduced global and regional connectivity in the paraquat group compared with vehicle controls.
- Both paraquat and glyphosate groups exhibited reduced reward-evoked BOLD responses, suggesting impaired dopaminergic circuit function.
- Immunohistology will assess dopaminergic markers ( $\alpha$ -synuclein, tyrosine hydroxylase) and microglial activation.
- Biomarker analyses will metabolic dysfunction and systemic inflammation to investigate herbicide-induced neuroinflammation and oxidative stress.

### Acknowledgement

- Thanks to EPA (U.S. Environmental Protection Agency) for providing Herbicidal neurotoxin
- Ekam Center for our MRI imaging technology
- Connectivity graph – Dr. Richard Ortiz, Northern Illinois
- Stay connected [runanlathamaheswa.n@northeastern.edu](mailto:runanlathamaheswa.n@northeastern.edu)

