RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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# In-Vivo Neuropathology: Detecting Site-Specific Changes in Neuroinflammation Post-treatment with Low Dose Neurotoxins

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## Abstract

Twenty-five percent of small molecules in CNS drug development fail in clinical trials due to neurotoxic complications, risking patients, time, and money. In-vivo Neuropathology (IVN) is a non-invasive MRI protocol for identifying site-specific changes in whole-brain BBB permeability and neuroinflammation. We administered TMT, MK-801, kainic acid, and BIA10-2474 in rats. Diffusion weighted imaging (DWI) was conducted, and the extracted apparent diffusion coefficient (ADC) values highlighted multiple brain areas as sites of critical neuroinflammation. The ability for IVN to follow disease progression longitudinally in the same rat offers a cost-effective and efficient alternative to the traditional tests for CNS neurotoxicity.

## Background

- BIA 10-2474 is an FAAH inhibitor meant to raise the endogenous levels of endocannabinoids to treat conditions such as neuropathic pain, psychiatric disorders, and neurodegenerative disorders. MR imaging of affected patients revealed significant damage to the thalamus and cerebral cortex.
- Trimethyltin (TMT) is a gold standard for CNS neurotoxicity, MK-801 is a NMDA antagonist and Kainic Acid is a glutamate agonist
- In Vivo Neuropathology (IVN) is a Diffusion Weighted Imaging (DWI) technique that tracks the diffusion of water throughout the brain by analyzing the apparent diffusion coefficients (ADC).

## Methods

### *Experimental Design*

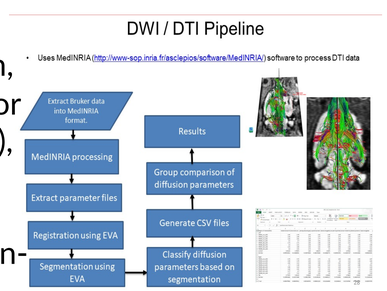
Female rats, five per group, were treated with either a single IP injection for trimethyltin chloride (7mg/kg), a single IP injection of MK-801 (0.5mg/kg), a single IP injection of kainic acid (10mg/kg) or 7-days gavage for BIA 10-2474 (1mg/kg). After administration, the rats were returned to their home cage to be left undisturbed until imaged 3 and 7 days post administration for trimethyltin and 7 days post administration for all other groups. Perfusion and brain extractions were performed for post-mortem analysis.

### *Imaging*

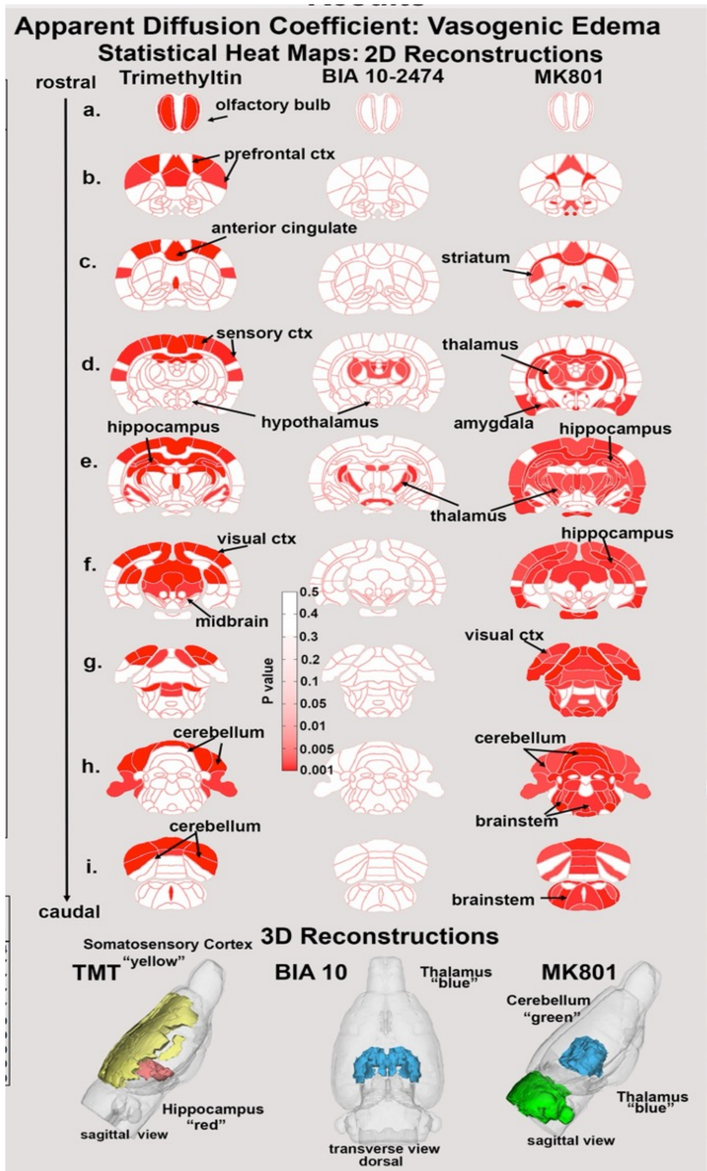
Imaging was carried out using a Bruker BioSpec 7.0T/20-cm USR horizontal magnet and a 20-G/cm magnetic field gradient. The RARE pulse sequence was used to collect high-resolution anatomical data. Diffusion weighted imaging (DWI) scans were collected.

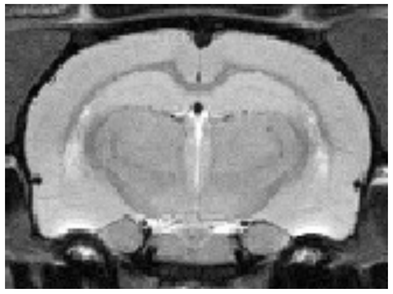
### *Imaging Analysis*

DWI analysis was carried out using the MATLAB (©Mathworks, USA) and MedINRIA (1.9.0; http://www.sop.inria.fr/asclepios/software/MedINRIA/index.php) softwares. After preprocessing for motion, the B0 image was co-registered with an MRI atlas. The map files for the apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial diffusivity (λ1), and radial diffusivity (RD) were used to calculate the average values for each region of interest. Statistical differences in the measures of DWI were determined using a Mann-Whitney U Test.

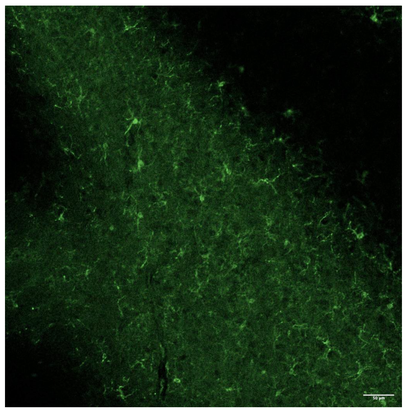



## Results



Anatomy Scan of 4 weeks 1 mg/kg BIA 10-2474



Cerebellar Immunofluorescence Portraying Microglia Activation following TMT

## Discussion

- Diffusion weighted imaging (DWI) was utilized to detect changes in gray matter associated with neuroinflammation
- IVN highlighted areas in the sensorimotor cortices (yellow) and hippocampus (red), thalamus (blue), and thalamus and cerebellar(green) regions, for TMT, BIA 10-2474, and MK801, respectively.
- Post-mortem histological validation of microgliosis for BIA 10-2474 and MK-801 is in progress

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