Quantitative T_2 mapping as a biomarker of neuropathology resulting from acute organophosphate intoxication in a rat model

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Objective

To evaluate brain T_2 maps as a potential quantitative biomarker in organophosphate (OP)-intoxicated rats to evaluate the effectiveness of therapeutics for attenuating OP-induced neuropathology.

Background

- OP nerve agents such as chemical warfare agents and OP pesticides represent a major societal public health issue.
- Acute OP intoxication triggers life threatening seizures and long-term neurologic consequences, including neuronal necrosis, edema, neuroinflammation, blood brain barrier dysfunction, and hemorrhage.
- Magnetic resonance imaging (MRI) T_2 (spin-spin) relaxation time constants are impacted by these pathologies.
- Conventional T_2 -weighted and diffusion MRI can interrogate brain lesions over time in a rat model of acute intoxication by OPs. However, quantification is not straightforward.

***Hypothesis*:** T_2 -mapping (T_2 decay quantification) will provide valuable information that would:

1. Characterize neuropathology resulting from OP-intoxication; and
2. Provide biomarkers to evaluate the effectiveness of therapeutics for attenuating OP-induced neuropathology.

Methods

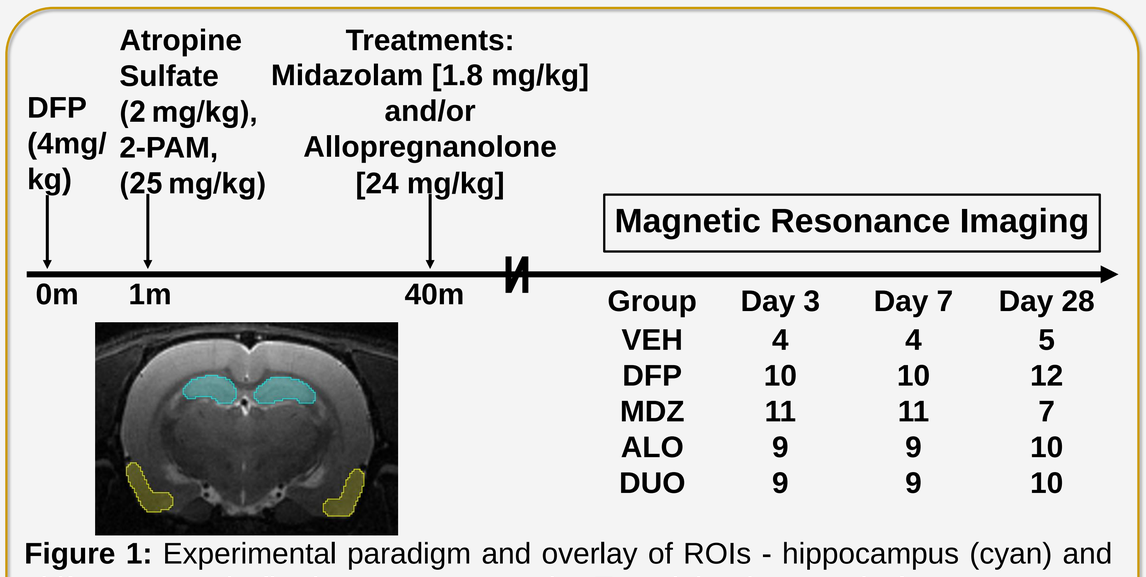

Figure 1: Experimental paradigm and overlay of ROIs - hippocampus (cyan) and piriform cortex (yellow) on a representative T_2-weighted anatomical scan.

***Animals and treatments*:** Adult Sprague Dawley rats were imaged at days 3, 7 and 28 after OP (using diisopropylfluorophosphate, DFP) intoxication. Rats were from one of the following groups:

- **VEH** (n=13): Vehicle controls
- **DFP** (n=32): DFP-exposed animals
- **MDZ** (n=29): DFP + midazolam (benzodiazepine anticonvulsant)
- **ALO** (n=28): DFP + allopregnanolone (a neurosteroid)
- **DUO** (n=28): DFP + MDZ + ALO

***Imaging Acquisition and Processing*:**

- T2-weighted 7T MRI scans were acquired using a rat brain phased array coil and a spin-echo pulse sequence with 15 echo times (TEs).
- Manual delineation of the hippocampus (H) and piriform cortex (PC) as regions-of-interest (ROIs) given their significance as targets of acute OP intoxication.
- Mono-exponential curve fitting in MATAB using the equation: $y = a.\exp(-x/b)$ was performed on MR images at all TEs, such that '**x**' : TE, '**y**' : signal intensity, '**b**' : sought T_2 relaxation time, and '**a**': constant representing signal gain or attenuation by the scanner and proton density, respectively. Curve fitting using 2 approaches:
  1. **Voxel-wise quantification**: curve fitting of intensity-TE curves for each voxel, providing a voxel-wise map of T_2 values
  2. **Regional quantification:** curve fitting to average voxel intensity values in each ROI at each TE and a curve fit to estimate T_2 value for each ROI.

Results

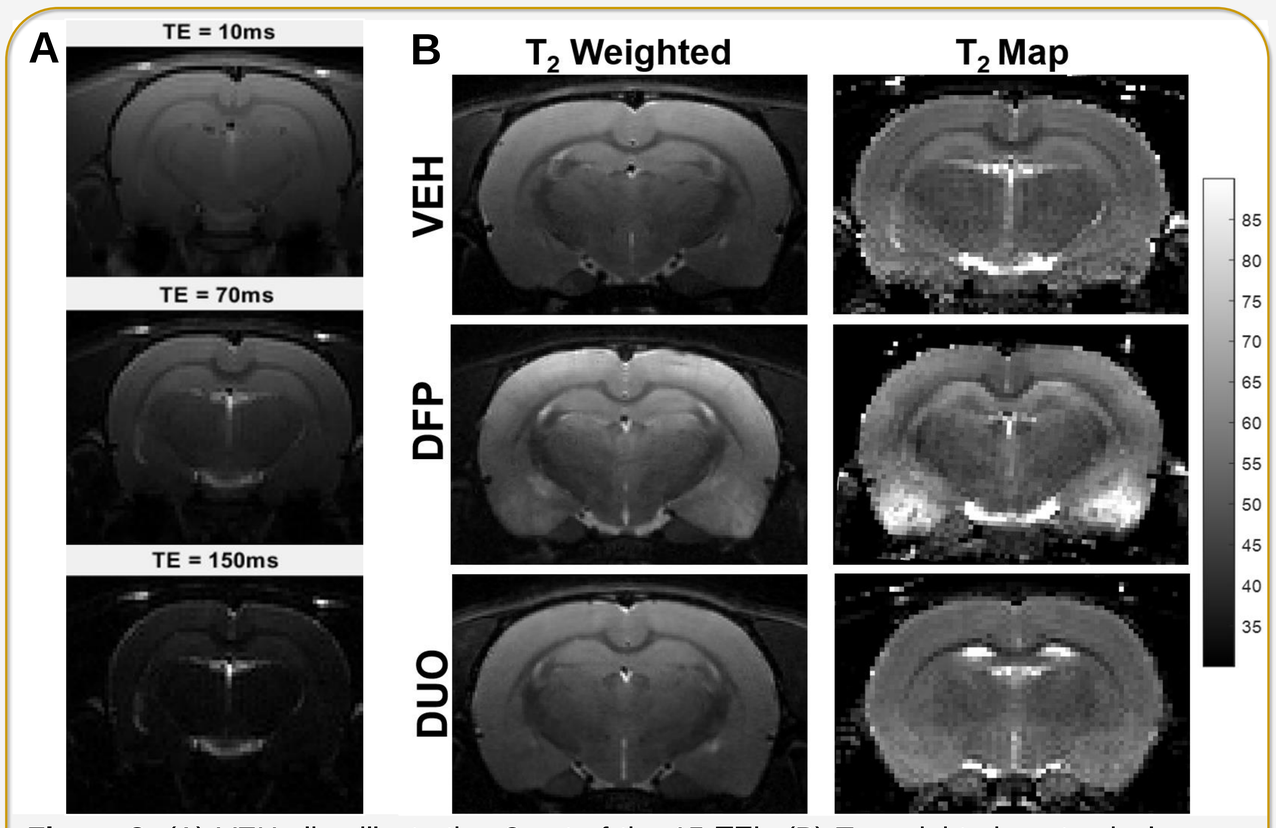

Figure 2: (A) VEH slice illustrating 3 out of the 15 TE's (B) T_2-weighted anatomical scans (left) and the corresponding T_2 maps (right) of animals from Day 3 with color bar in ms;

VEH T_2 values were within the range reported in the literature

⇒ *voxel-wise*- H: 53.8 ms, PC: 57.86 ms

⇒ *regional*- H: 54.3 ms, PC: 55.24 ms

- **In general, T_2 values were longest on day 3 and decreased with time.**
- **OP-intoxicated rats (DFP group) had the longest T_2 values**

  ⇒ *voxel-wise- H: 57.23 ms, PC: 71.21 ms*

  ⇒ *regional- H: 57.4 ms, PC: 59.09 ms*
- **All interventions resulted in a reduction in average T_2 values compared to the DFP group ($p<0.05$)**

  ⇒ *voxel-wise*- H: 54.02 ms, PC: 62.37 ms

  ⇒ *regional*- H: 54.5 ms, PC: 55.44 ms
- The pattern of distribution of T_2 values was relatively uniform in regions across days and groups. The voxel-wise quantification showed a larger variation in T_2 values within ROIs than regional quantification, suggestive of intra-regional heterogeneity of neuronal damage.

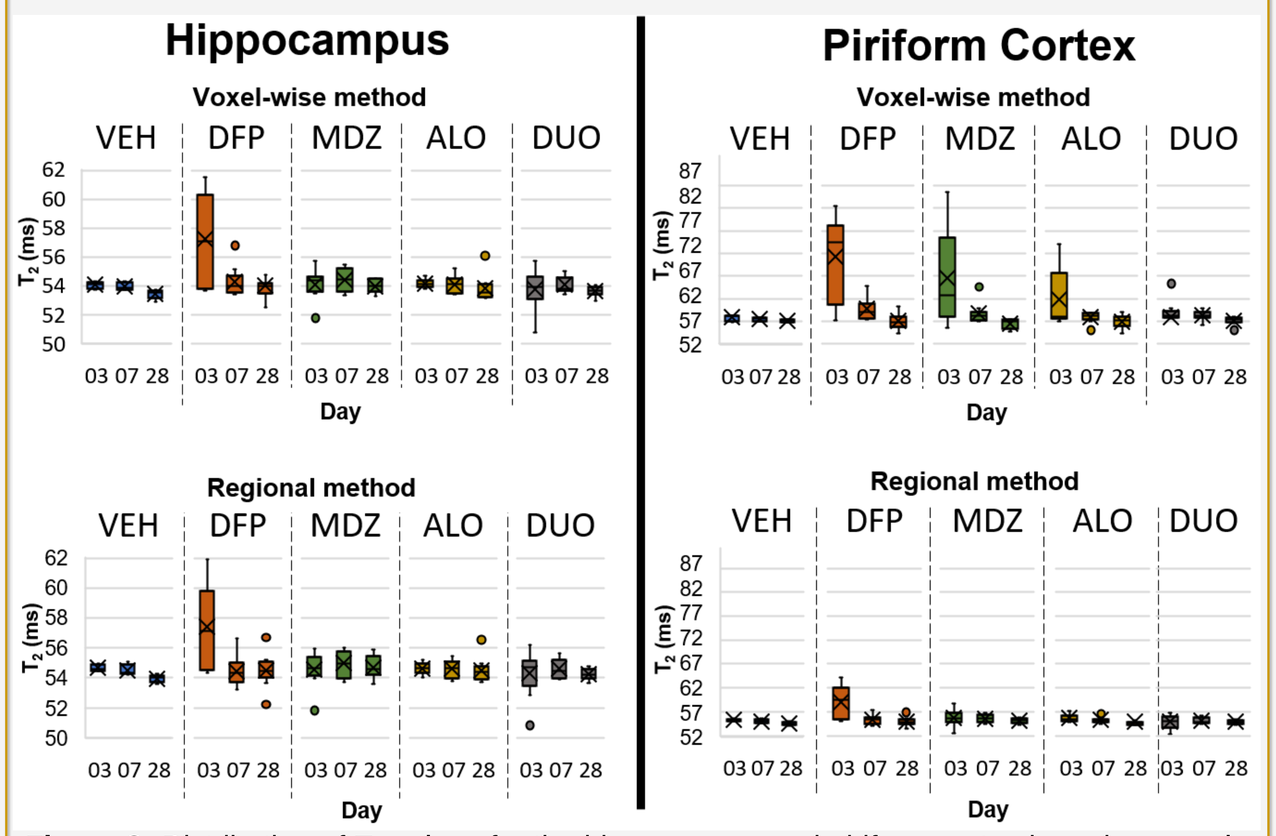

Figure 3: Distribution of T_2 values for the hippocampus and piriform cortex based on voxel-wise (top row) and regional (bottom row) quantification methods, arranged by treatment group and time post exposure.

Conclusions

This study demonstrates the potential of T_2 mapping as a quantifiable biomarker to longitudinally track neuropathology following OP-intoxication, and to assess the impact of therapies.

Future work will include validation of the methods against histology and diffusion MRI metrics.

Acknowledgements

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