Determining the Efficacy of Intranasal Delivery of the Superoxide Scavenger TEMPOL Following TBI

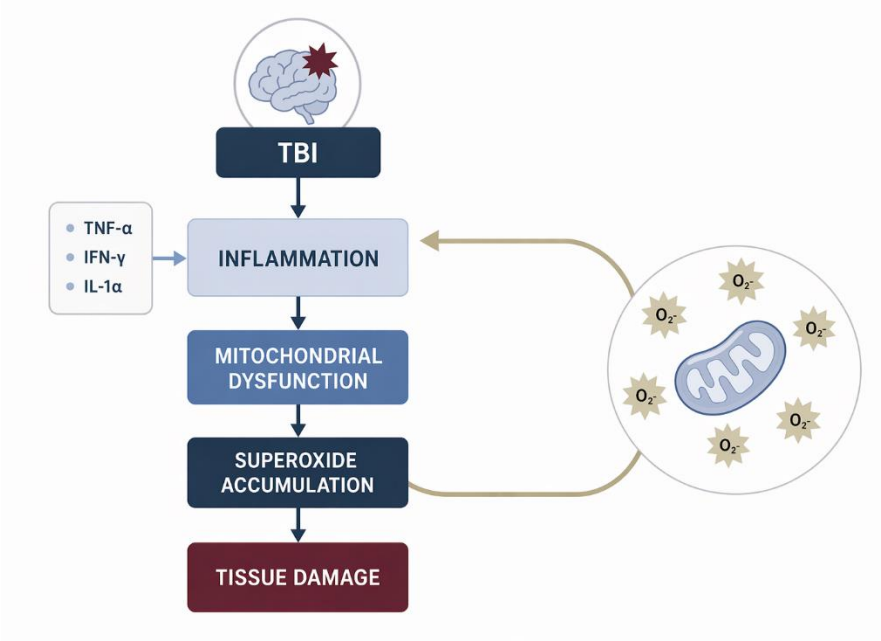
Jack Hutcheson, PhD

Aug 6, 2026

Disclaimer

- The views expressed in this presentation reflect the results of research conducted by the author and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of War, nor the U.S. Government.
- The experiments reported herein were conducted in compliance with the Animal Welfare Act and per the principles set forth in the “Guide for the Care and Use of Laboratory Animals, Eighth Edition”, The National Academies Press, 2011.
- Neither the Defense Health Agency, any other component of the Department of War nor the U.S. government has approved, endorsed or authorized this product. No Federal endorsement of any manufacturer is intended.
- This work is supported by funding from DHA Restoral and Oak Ridge Institute for Science and Education.

Introduction: Basics of Traumatic Brain Injury (TBI)



CDC:
>586 TBI-related hospitalizations per day

“signature wound” of recent conflicts

>75% report pain chronic

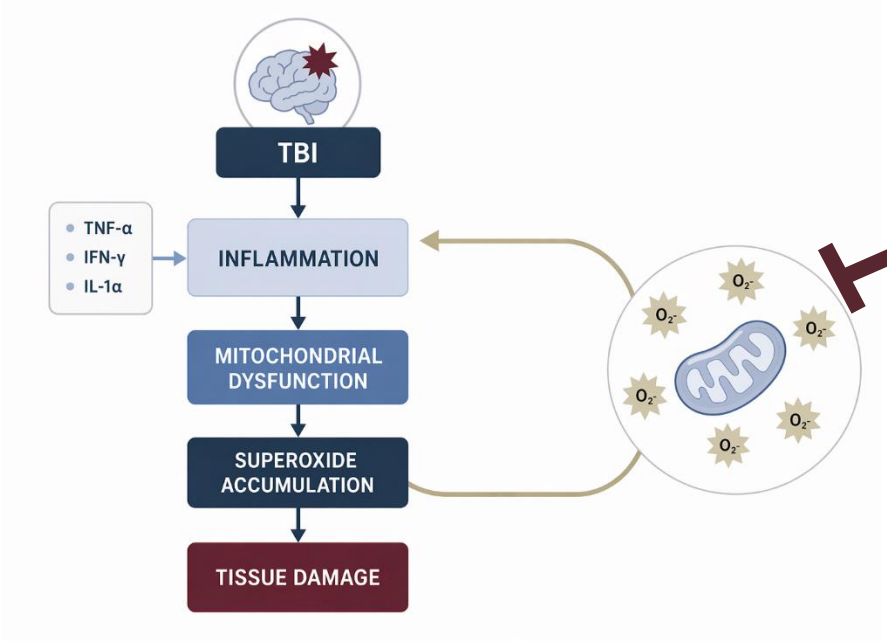
Primary Injury:

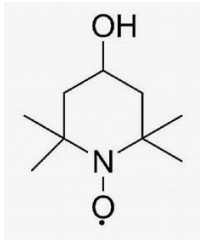
- Direct damage to tissues and hemorrhage

Secondary Injury:

- Rapid cascade beginning within 10 minutes of injury
- Creates a positive feedback loop

Introduction: 4-hydroxy-TEMPO (TEMPOL)





Superoxide Dismutase (SOD) Mimetic

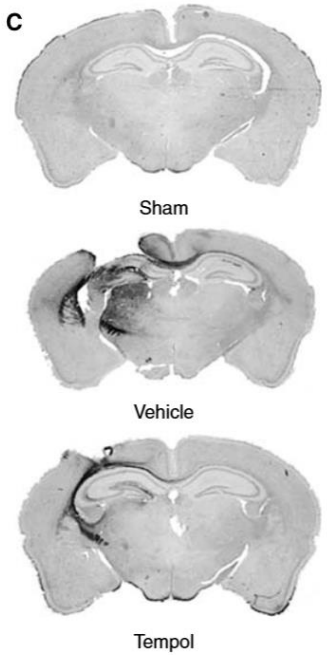
Scavenges Superoxides

- Breaks positive feedback loop

Additional Benefits:

- Blood Brain Barrier Repair
- Mitochondrial Damage Reduction
- Cytoskeletal Damage Reduction

Previous IV TEMPOL Treatment Results



Hall et al.

Significant reduction in neurodegeneration

Deemed ineffective for clinical application because of IV placement time in active combat zone

QUESTION: What if it was administered intranasally?

Intranasal Delivery

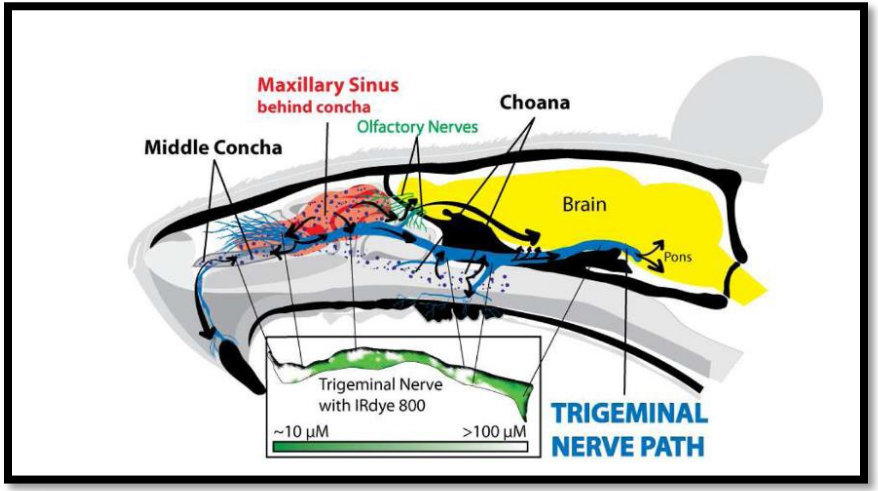
Rapid Delivery to Brain

Improved Delivery Concentration

Easy administration

Time is vital in combat situations or mass casualty events

- Find Medic
- Secure the battlefield
- Triage patients
- Presence of Supplies



Published in final edited form as:
Mol Pharm. 2010 June 7; 7(3): 884–893. doi:10.1021/mp100029t.

Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures

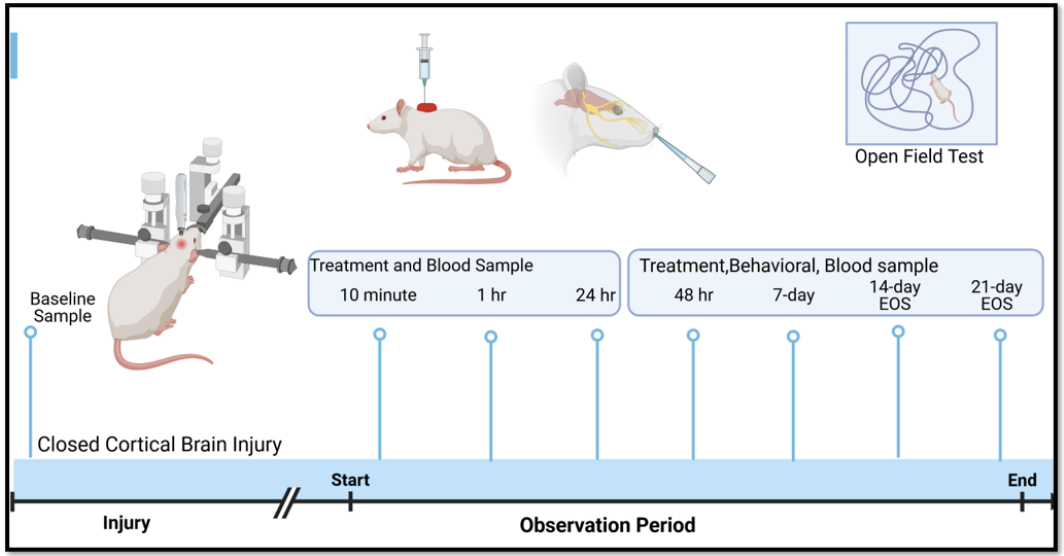
Neil J. Johnson, **Leah R. Hanson**, and **William H. Frey II***

Research Questions

Is **IN** administration of TEMPOL **as effective** as **IV** TEMPOL for improving TBI recovery biomarkers?

Is **IN** TEMPOL as effective as IV TEMPOL for improving TBI related anxiety symptoms?

Experimental Design



Moderate closed cortical impact

Wistar Rat

10 mg/kg TEMPOL in Lactate Ringers (LR)

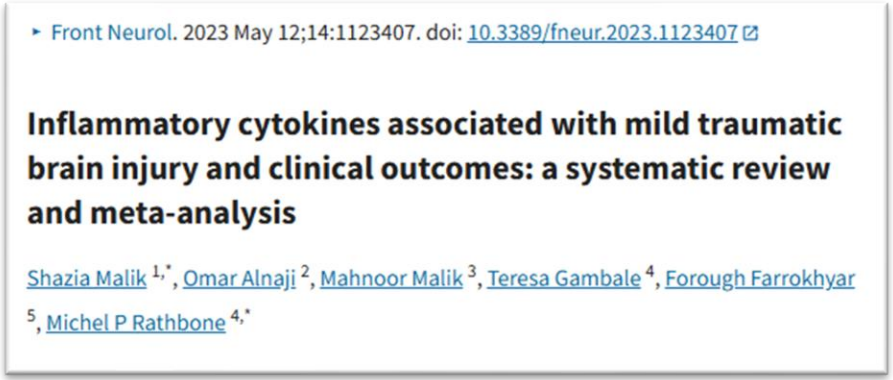
- Intravenous (IV)
- Intranasal (IN)
- Controls with LR only

Common Serum Biomarkers:

- Brain Derived Neurotrophic Factor
- TNF-α, IFN-γ, IL-10

Open Field Anxiety Test

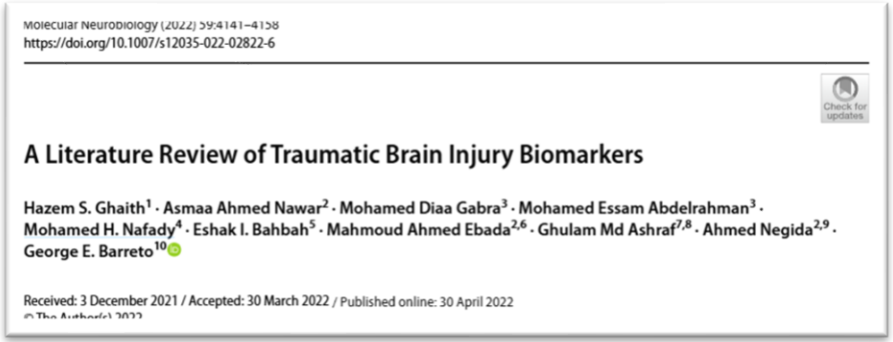
High Variability in post-TBI Biomarkers



Front Neurol. 2023 May 12;14:1123407. doi: 10.3389/fneur.2023.1123407

Inflammatory cytokines associated with mild traumatic brain injury and clinical outcomes: a systematic review and meta-analysis

Shazia Malik [1,*], Omar Alnaji [2], Mahnoor Malik [3], Teresa Gambale [4], Forough Farrokhyar [5], Michel P Rathbone [4,*]



Molecular Neurobiology (2022) 59:4141–4158
https://doi.org/10.1007/s12035-022-02822-6

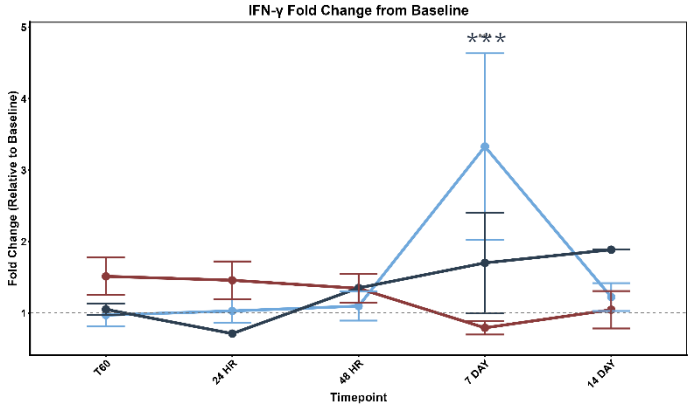
A Literature Review of Traumatic Brain Injury Biomarkers

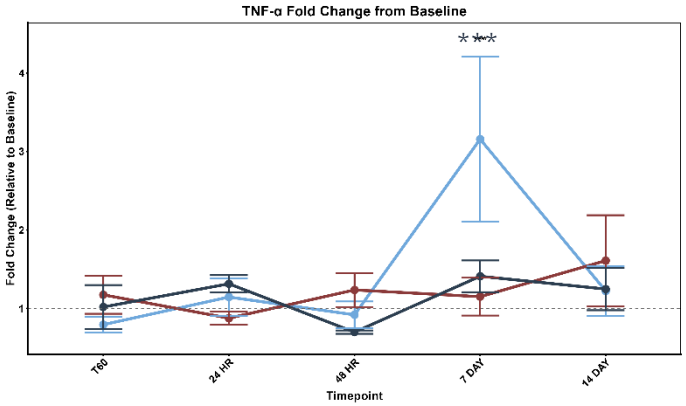
Hazem S. Ghaith[1] · Asmaa Ahmed Nawar[2] · Mohamed Diaa Gabra[3] · Mohamed Essam Abdelrahman[3] · Mohamed H. Nafady[4] · Eshak I. Bahbah[5] · Mahmoud Ahmed Ebada[2,6] · Ghulam Md Ashraf[7,8] · Ahmed Negida[2,9] · George E. Barreto[10]

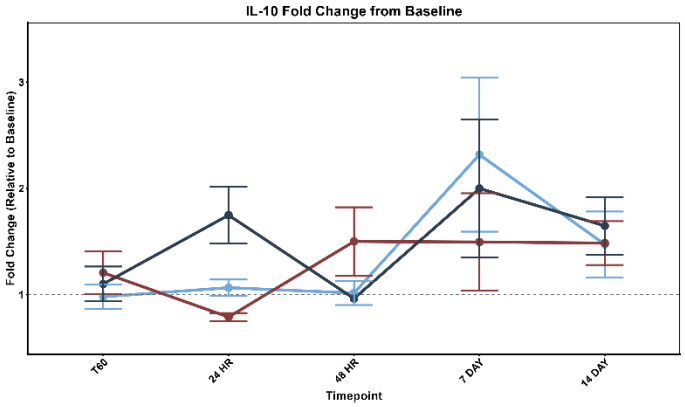
Received: 3 December 2021 / Accepted: 30 March 2022 / Published online: 30 April 2022

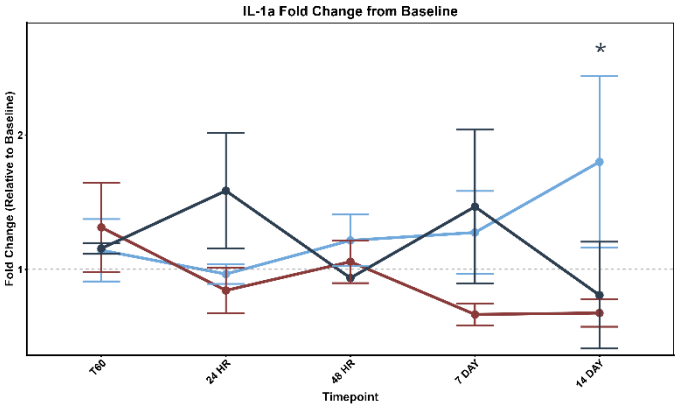
Meta-Analyses of TBI biomarkers report >80% heterogeneity in patients

Inflammatory Biomarker Results





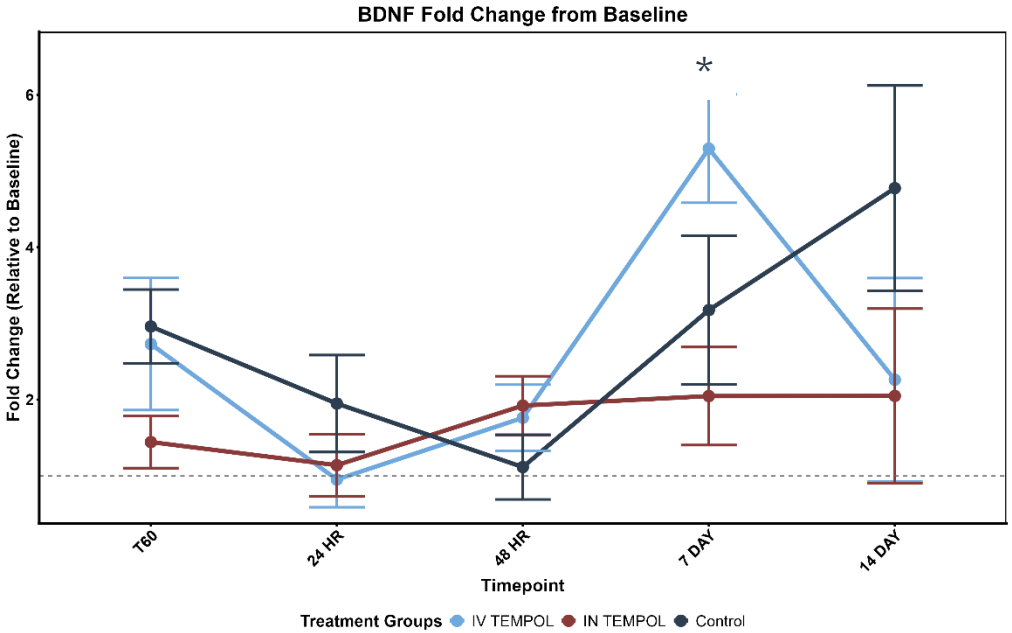




Treatment Groups

- IV TEMPOL
- IN TEMPOL
- LR Control

Brain Derived Neurotrophic Factor (BDNF) Results



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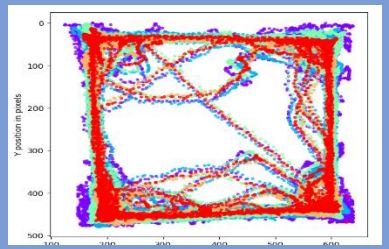
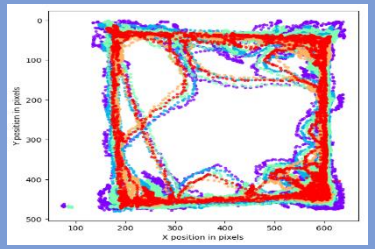
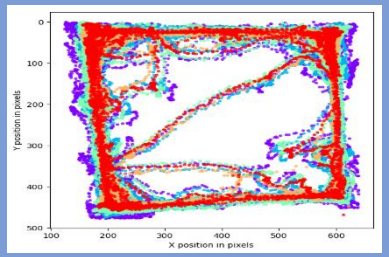
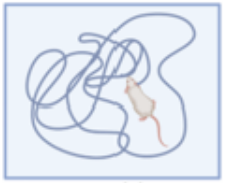
Takeaway: Inconclusive

- p= 0.06 trending toward significance overall
- IN groups appear to be more stable compared to other groups, particularly at 7 and 14 days
- More information outside of biomarkers are essential

Open Field Test: Anxiety Measures

	IV TEMPOL	IN TEMPOL	Control
Baseline Pre TBI			
24 Hours Post TBI			
14 Days Post TBI			

10 Minutes



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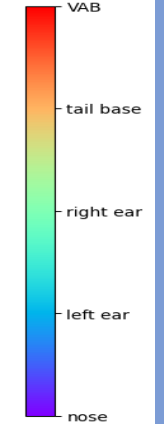

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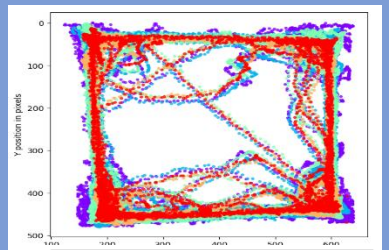
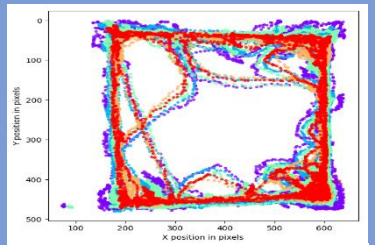
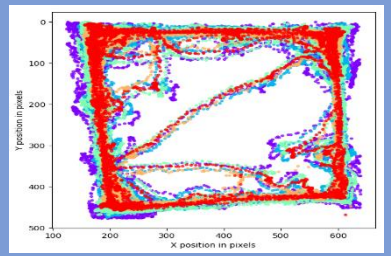
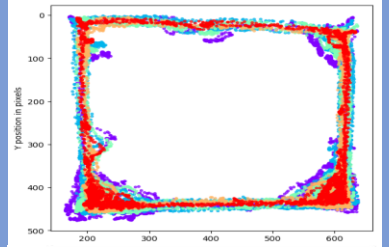
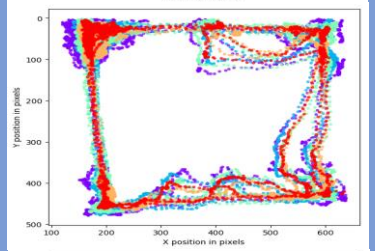
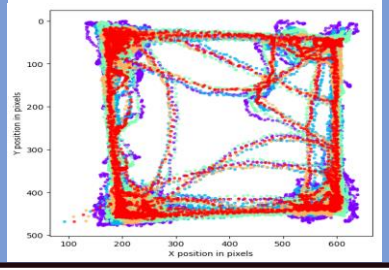
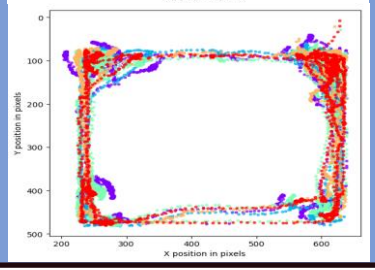
Baseline Pre TBI			
24 Hours Post TBI			
14 Days Post TBI			

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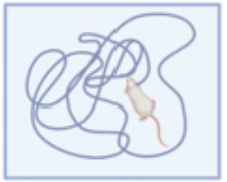

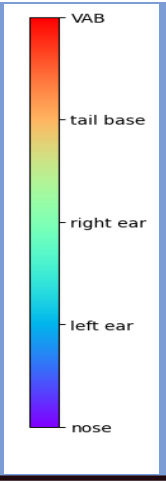

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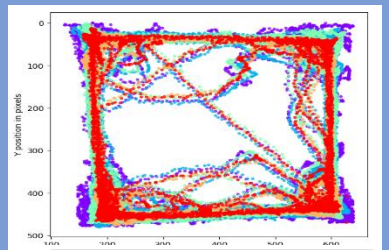
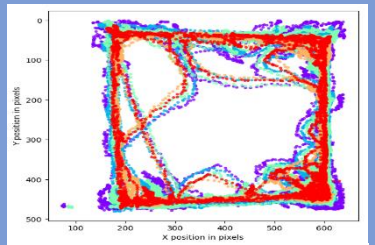
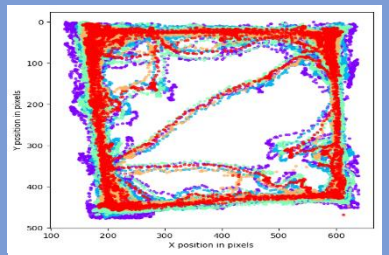
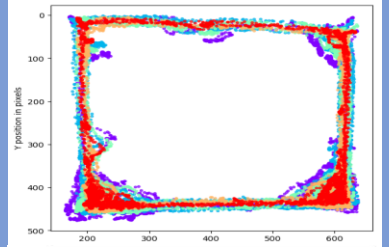
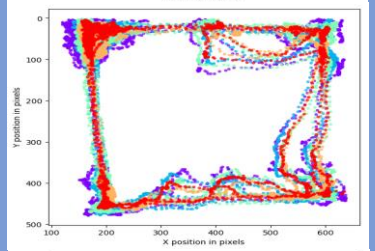
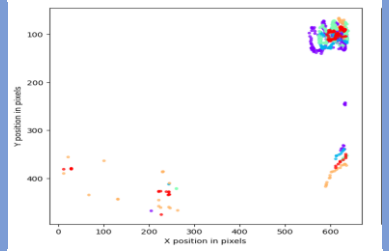
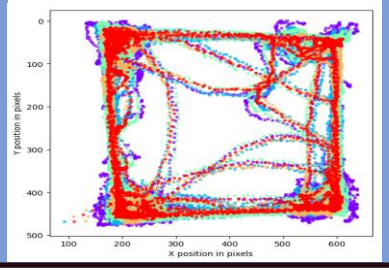
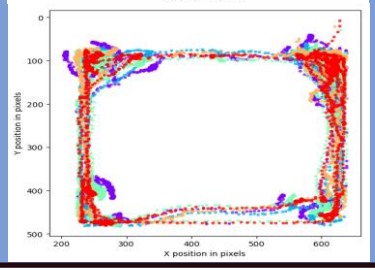
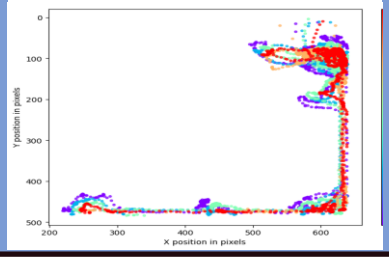
Baseline Pre TBI			
24 Hours Post TBI			
14 Days Post TBI			

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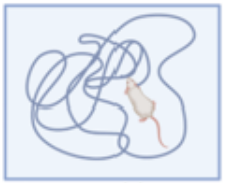
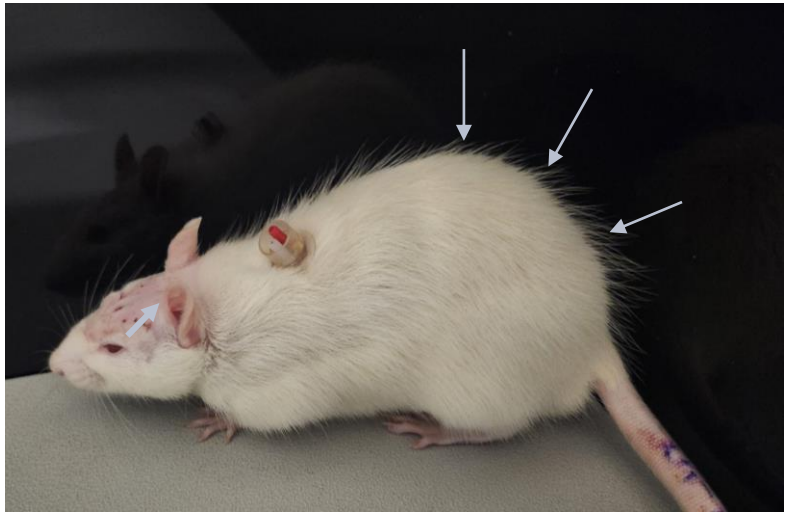
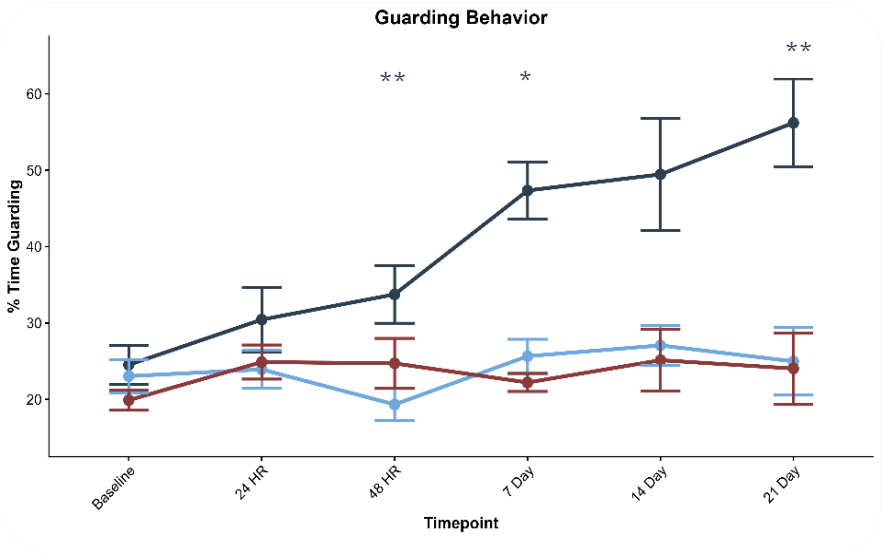


Deep Lab Cut Behavioral Measurements





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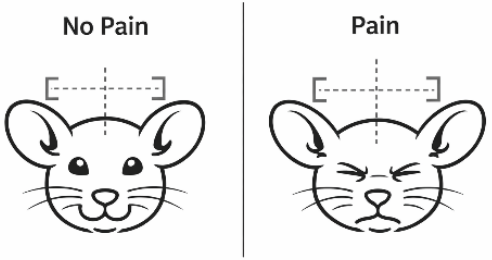

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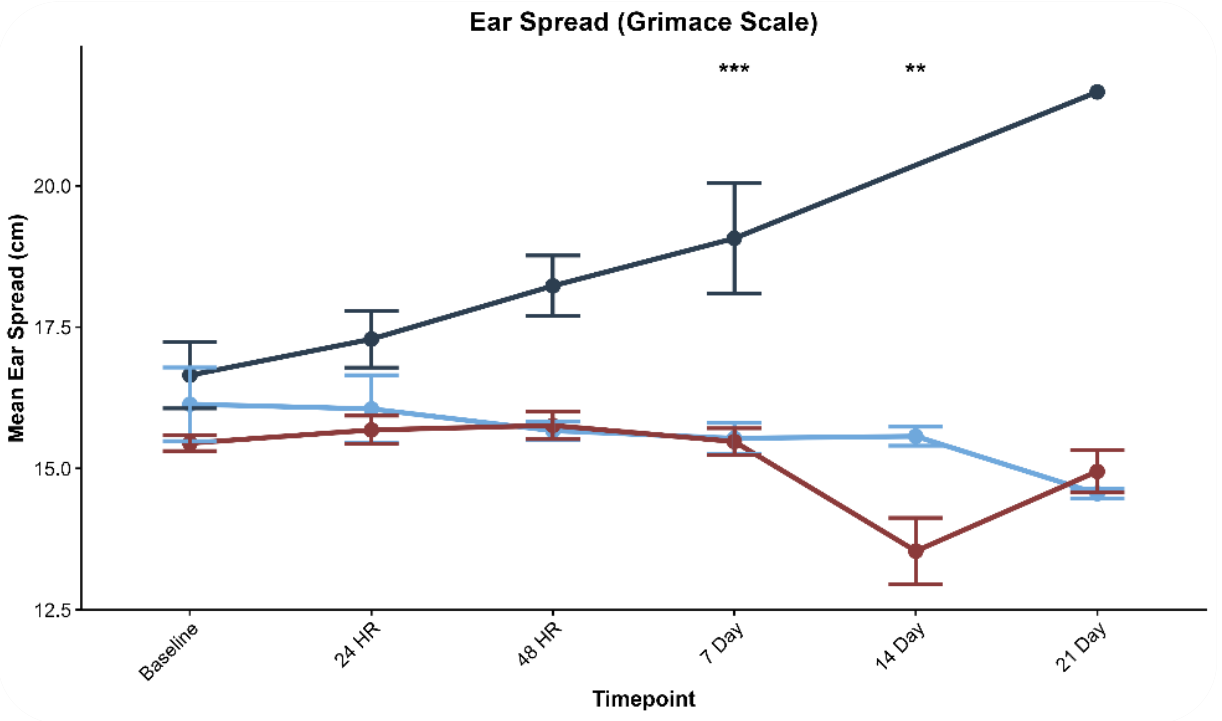


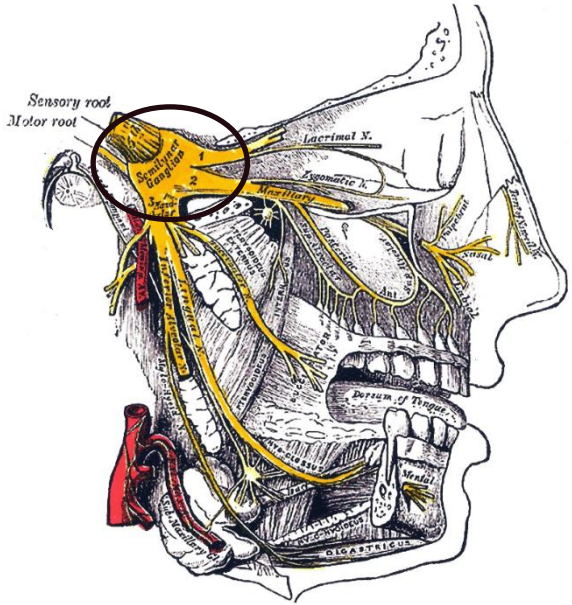
Research Questions

Is **IN** administration of TEMPOL as effective as **IV** TEMPOL for improving TBI recovery biomarkers?

Is **IN** TEMPOL as effective as **IV** TEMPOL for improving TBI related anxiety symptoms?

Is there a difference in oxidative damage molecules in trigeminal ganglia between IN and IV treatments?

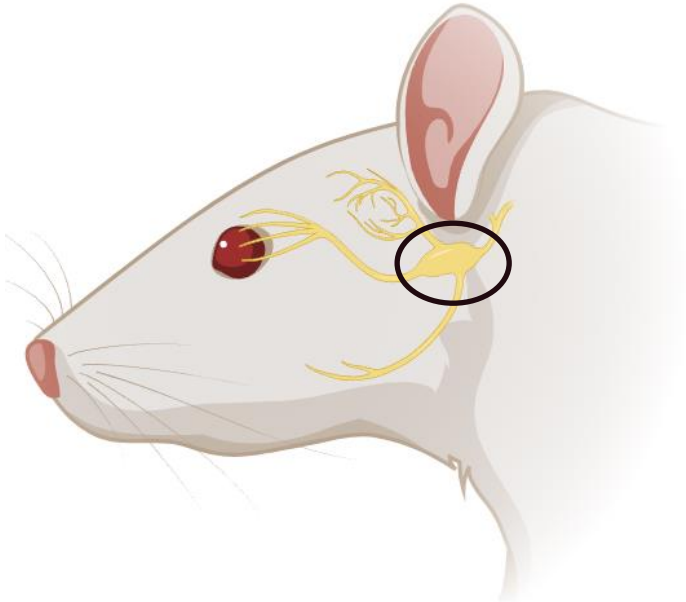
Trigeminal Ganglia



Facial Innervation

Eyes, nose, jaw

Associated with Orofacial and Head Pain



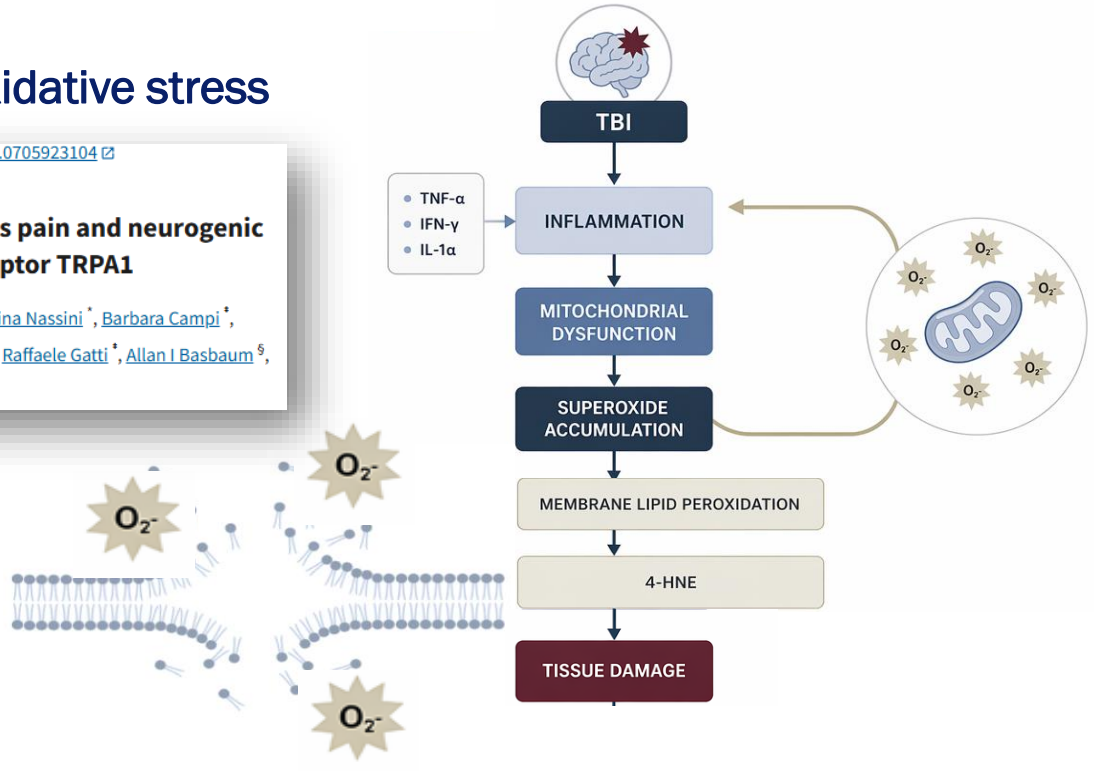
4-Hydroxynonenal (4-HNE)

Secondary Measurement of oxidative stress

Proc Natl Acad Sci U S A. 2007 Aug 7;104(33):13519–13524. doi: 10.1073/pnas.0705923104

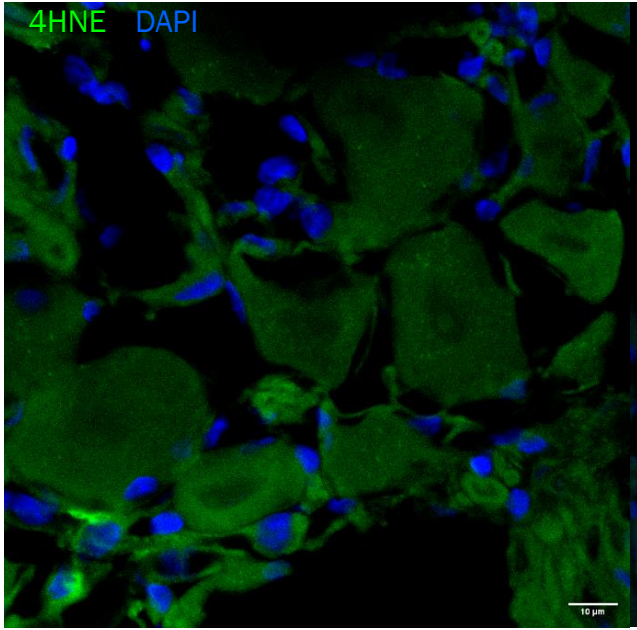
4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1

Marcello Trevisani [*], Jan Siemens [†], Serena Materazzi [*], Diana M Bautista [†], Romina Nassini [*], Barbara Campi [‡], Noritaka Imamachi [§], Eunice Andrè [‡], Riccardo Patacchini [¶], Graeme S Cottrell [‖], Raffaele Gatti [‡], Allan I Basbaum [§], Nigel W Bunnett [‖], David Julius [†,**], Pierangelo Geppetti [*,‡,**]

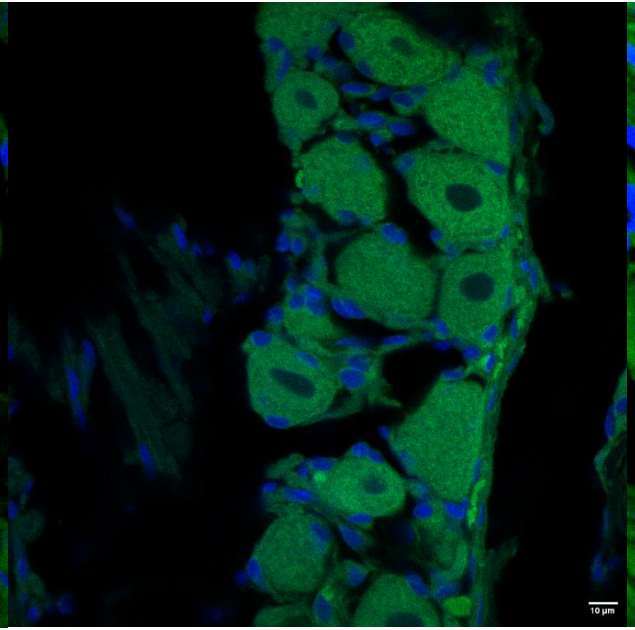


4HNE Expression in Trigeminal Ganglion

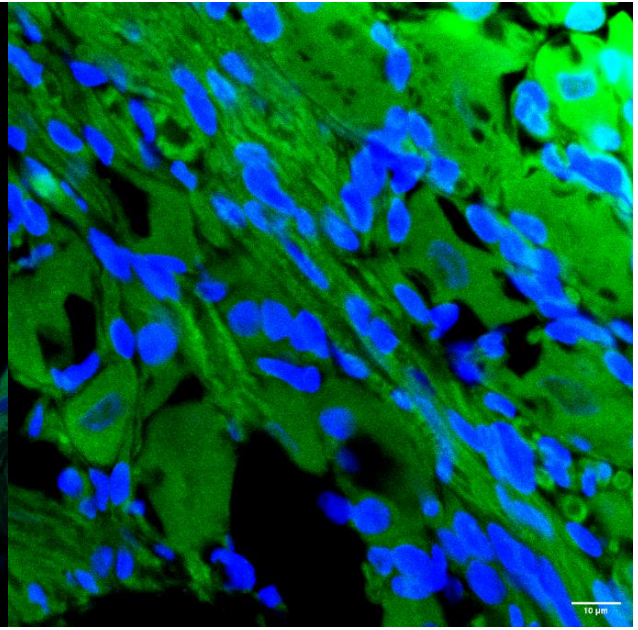
IV



IN



Control



Conclusions

Is IN administration of TEMPOL as effective as IV TEMPOL for improving TBI recovery biomarkers?

It's complicated

Is IN TEMPOL as effective as IV TEMPOL for improving TBI related anxiety symptoms?

Inconclusive, but pain looks likely

Is there a difference in oxidative damage molecules in trigeminal ganglia with and without TBI?

Very Promising

Intranasal Delivery

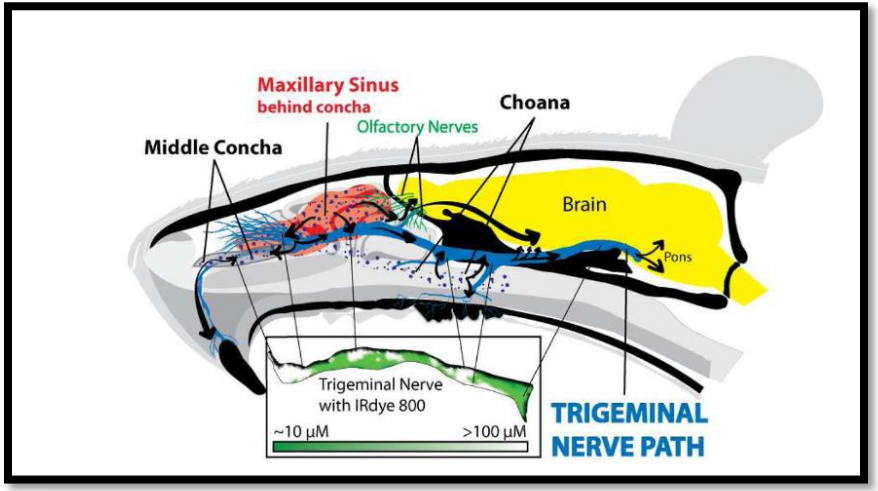
Rapid Delivery to Brain

Improved Delivery Concentration

Easy administration

Bypasses first pass metabolism

- Lowers secondary organ toxicity
- Improves uptake



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Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures

Neil J. Johnson, **Leah R. Hanson**, and **William H. Frey II***

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59MDW/ST

- Kimberly Baker
- Melody Sandoval
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- Victoria DeLeon
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University of Texas San Antonio

- Emily Holder
- Lindsey Macpherson

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- Erin Lavik