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A rat model of super-refractory status epilepticus

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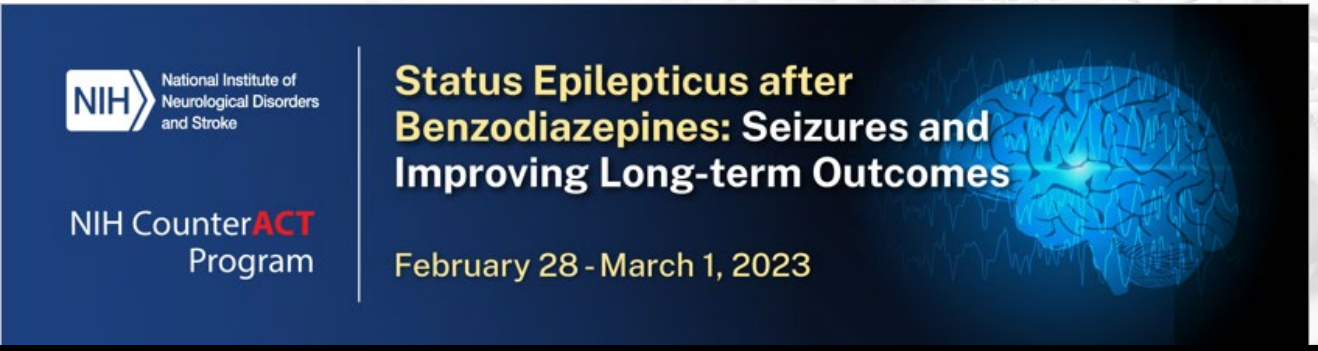

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Disclaimers

- This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of NIH.
- The research described was supported by interagency agreements (AOD18013/AOD19020/ AOD20020/AOD21005-001-00000) between the NIH Office of the Director (OD) and the U.S. Army Medical Research Institute of Chemical Defense under the oversight of the Chemical Countermeasures Research Program (CCRP) within the Office of Biodefense Research (OBRS) at the National Institute of Allergy and Infectious Diseases (NIAID/NIH).
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- The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended

Disclosure

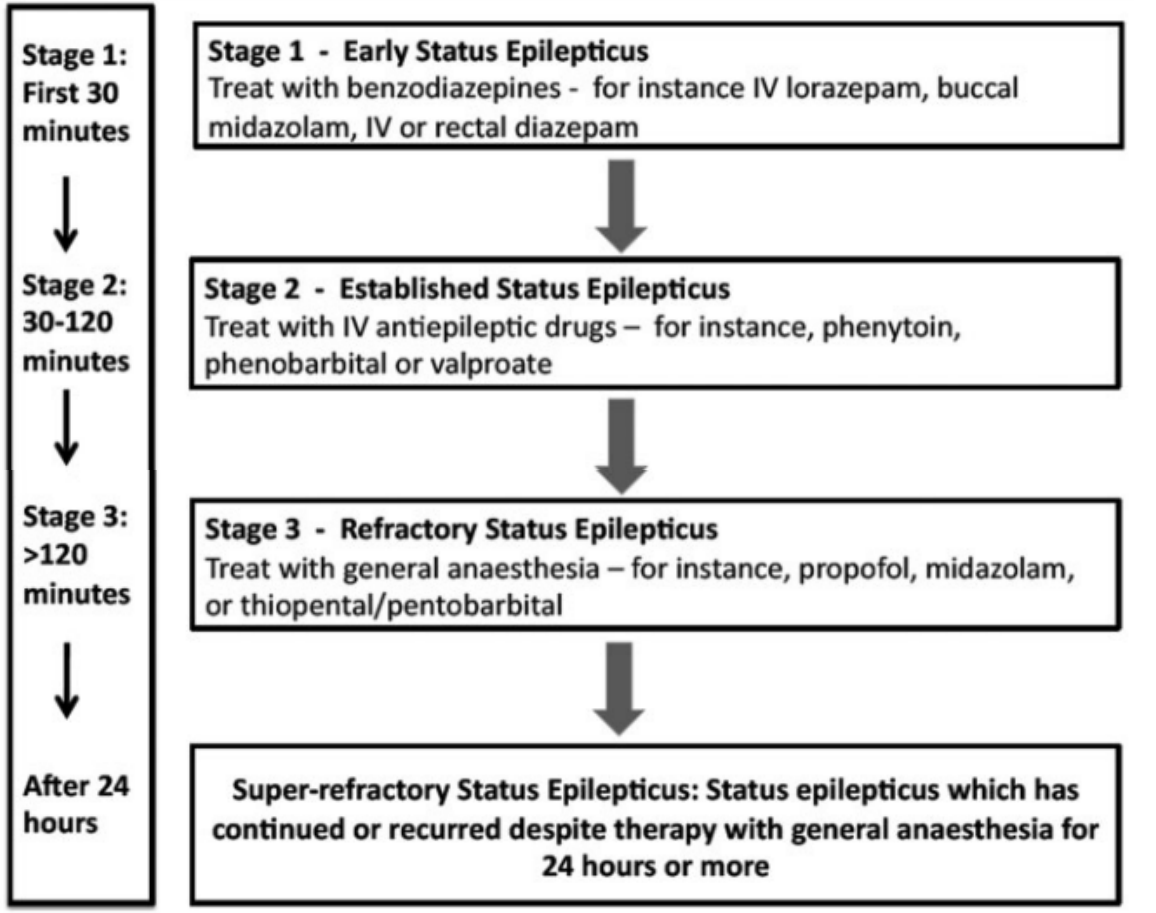
- This certifies that I, Hilary McCarren, have no financial relationship that is relevant to the subject matter of the presentation.

Background

- Nerve agent poisoning causes seizure activity as a result of excess acetylcholine, which builds up after inhibition of the enzyme acetylcholinesterase
  - Unless quickly stopped pharmacologically, these seizures rapidly progress to status epilepticus
- Survivors of severe nerve agent exposure will require hospitalization
- A definitive plan for rapid and aggressive treatment is the best way to prevent long-term neurological consequences

Rodent Model Goals

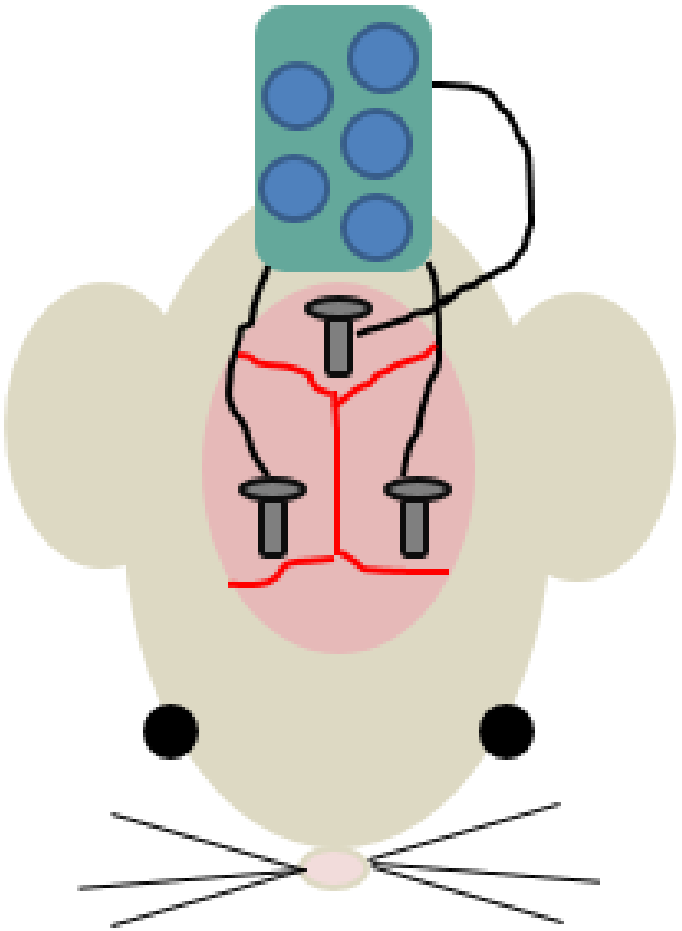
- Combine pre-hospital nerve agent countermeasures with clinical guidelines for treatment of SE
- Provide responsive pharmacological and supportive care
- Evaluate long-term behavior and pathology as surrogate measures for quality of life



Shorvon & Ferlisi, *Brain* 2011

Methodology

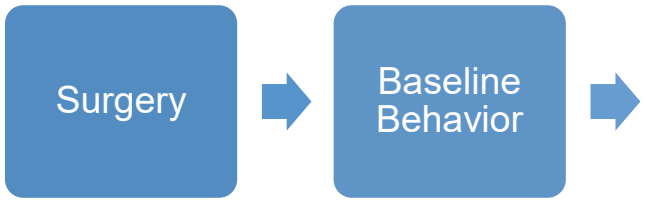
- Male Sprague Dawley rats
- Pre-implanted with jugular vein catheter for IV access
- Bilateral cortical EEG electrodes with cerebellar ground
- Surgery ~1 week before exposure



Surgery

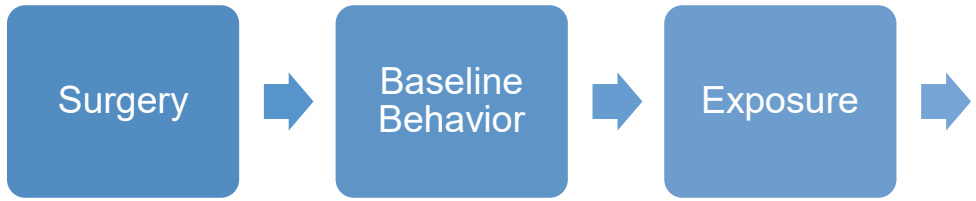
Methodology

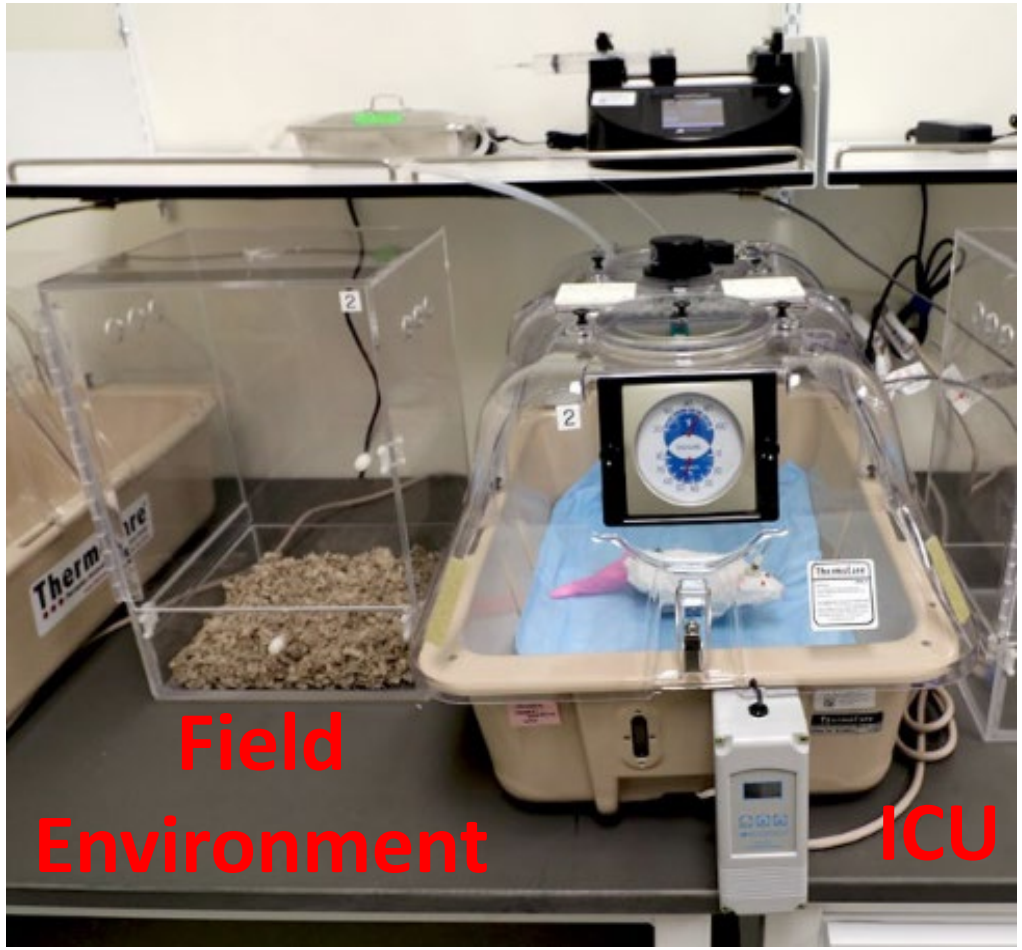
- Open field test
- Elevated plus maze
- 1 x 5 min trials
- Assessed 3 days post-surgery



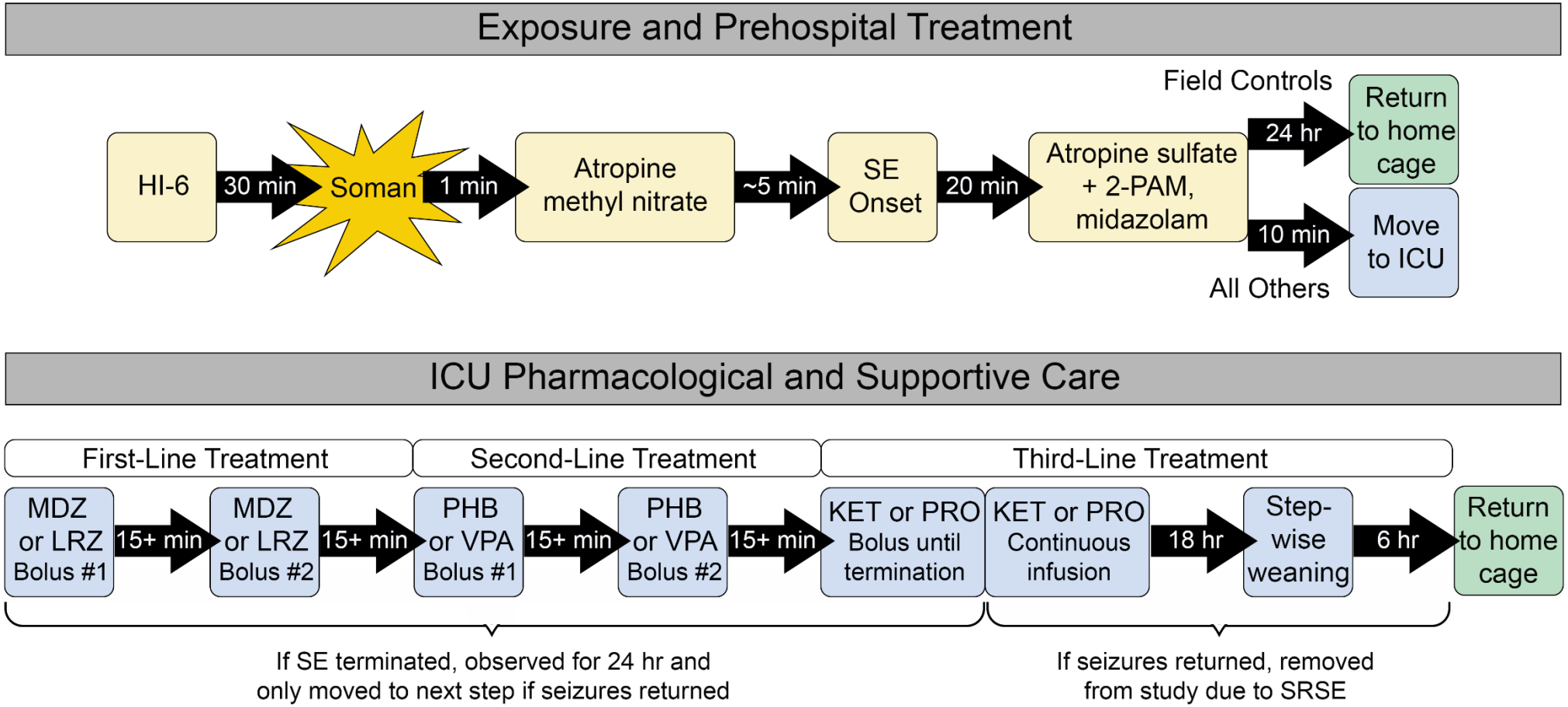
Methodology

- Pre-hospital treatments delivered IM, model CHEMM guidelines
  - Atropine
  - 2-PAM
  - Midazolam
- 2 controls: Field and ICU





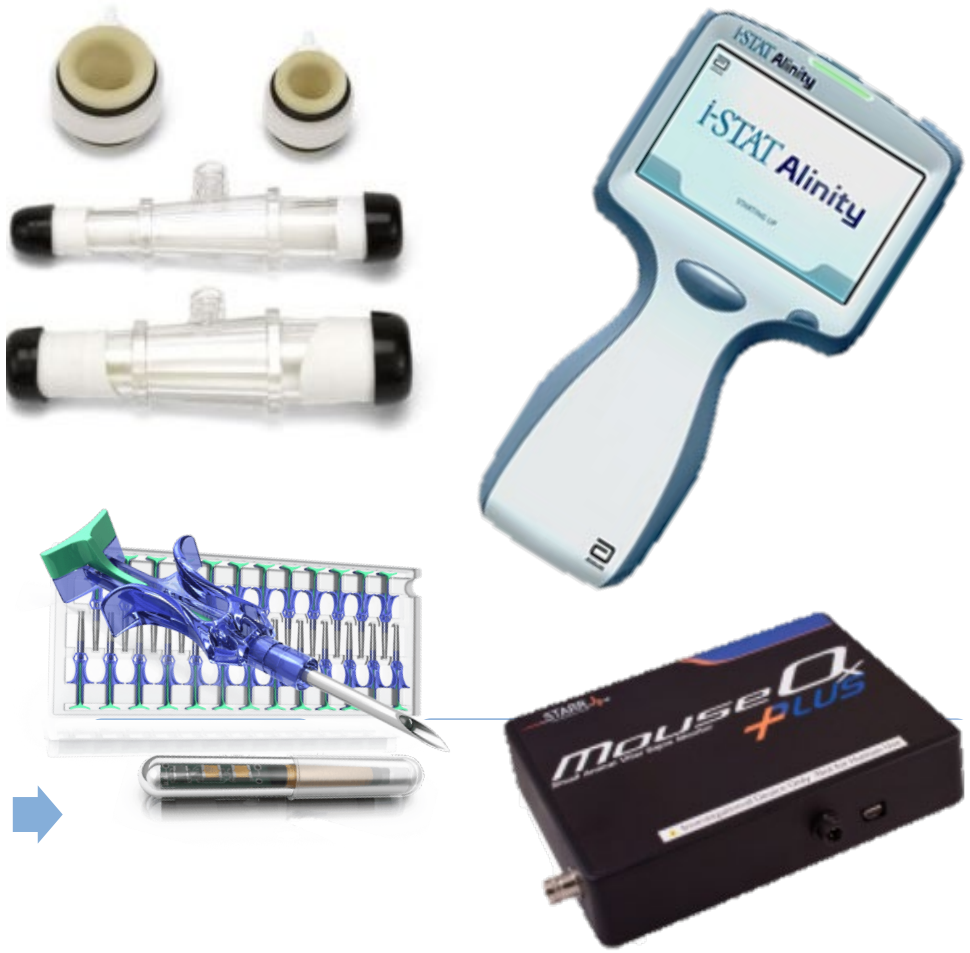
Methodology



Morgan, et al., *Frontiers in Neuroscience* 2021

Methodology

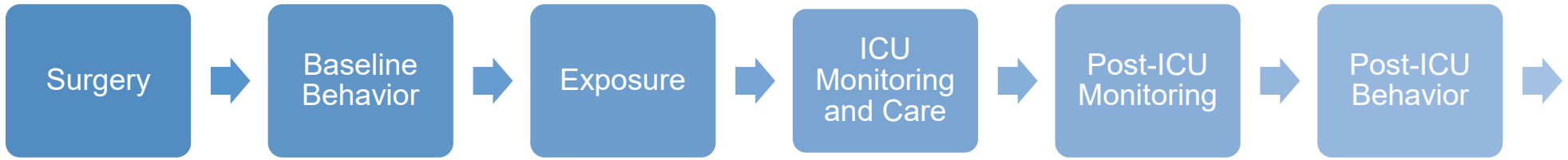
- Pulse oximetry, blood pressure, temperature, blood chemistry
- IV pharmacological care is responsive, randomly pre-assigned
- Supportive oxygen and heat as indicated, additional fluids and atropine



Surgery → Baseline Behavior → Exposure → ICU Monitoring and Care →

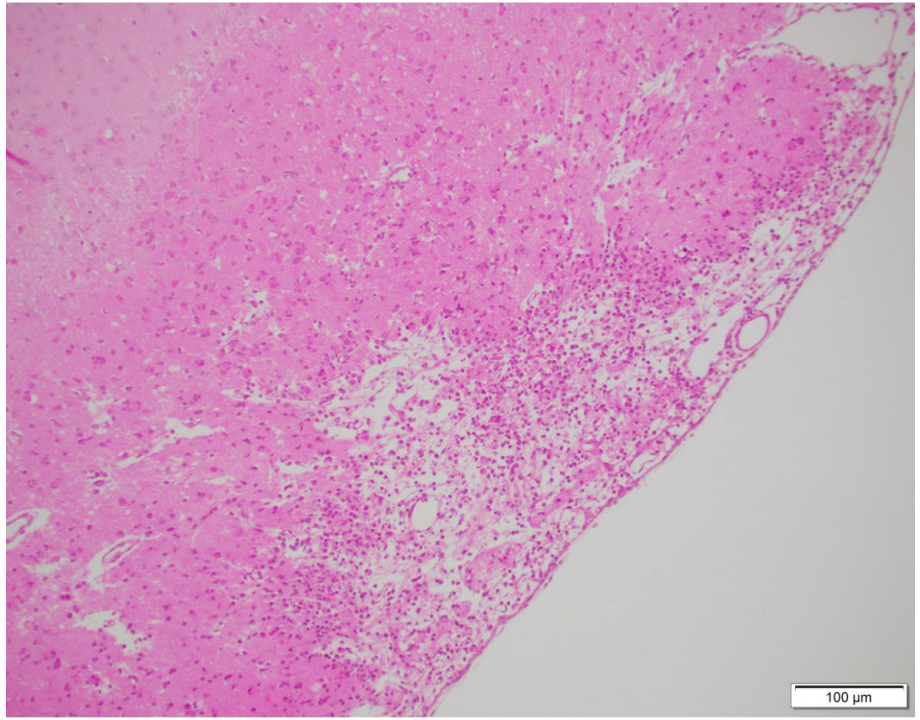
Methodology

- Return to home cage after 24 hours (controls) or definitive resolution of SE
- Super-refractory SE = early end point
- Daily weighing and scoring for 10 days post-exposure



Methodology

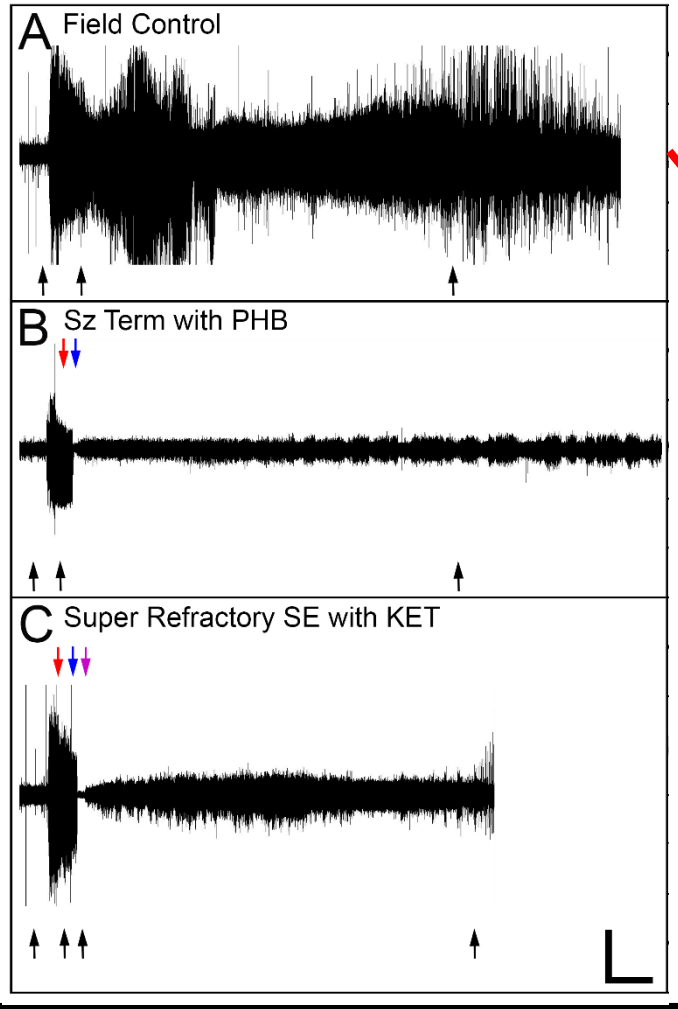
- Second set of behavioral tests performed 9 days after exposure
- Perfusion 11 days post-exposure
- H&E scoring by pathologist in vulnerable brain regions

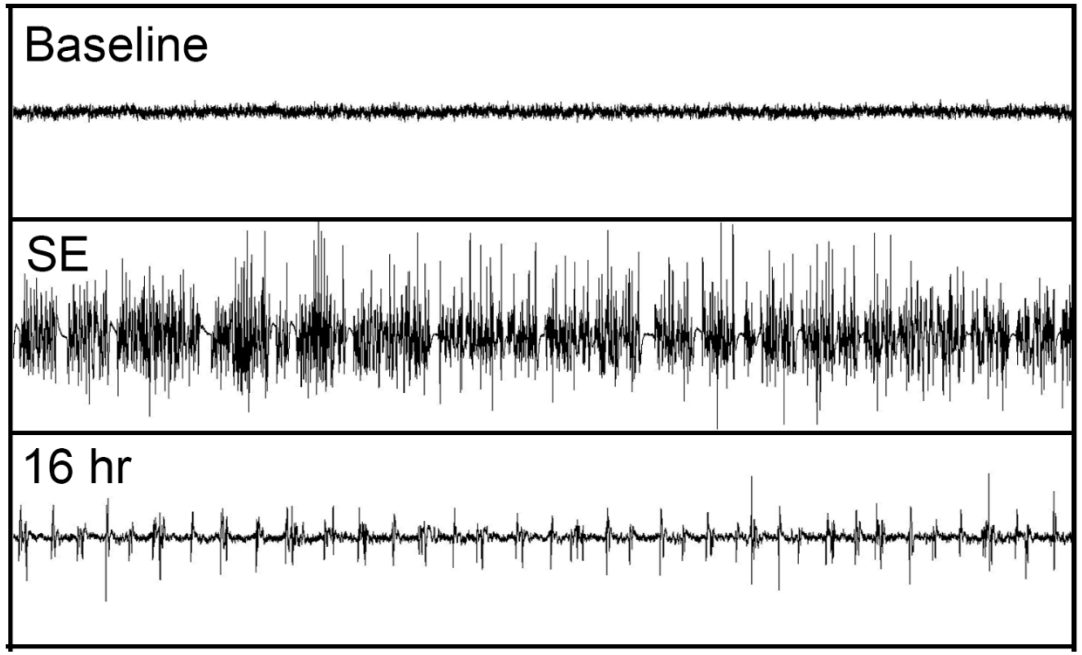


Standard Treatment Protocol Outcomes

	Drug	Total # of rats	Initial SE Control	Fisher's p value	Lasting SE Control	Fisher's p value	Survival	Fisher's p value
Control	Field Control	28	3 (11%)	.999	1 (4%)	.999	9 (32%)	.739
	ICU Control	16	2 (13%)		1 (6%)		4 (25%)	
1st Line	Midazolam	69	7 (10%)	.536	0 (0%)	.999	62 (90%)	.767
	Lorazepam	63	4 (6%)		0 (0%)		58 (92%)	
2nd Line	Phenobarbital	77	43 (56%)	.036*	15 (19%)	.001**	48 (62%)	.154
	Valproate	43	15 (35%)		0 (0%)		33 (77%)	
3rd Line	Propofol	31	31 (100%)	.999	0 (0%)	.999	11 (35%)	.288
	Ketamine	35	35 (100%)		1 (3%)		8 (23%)	

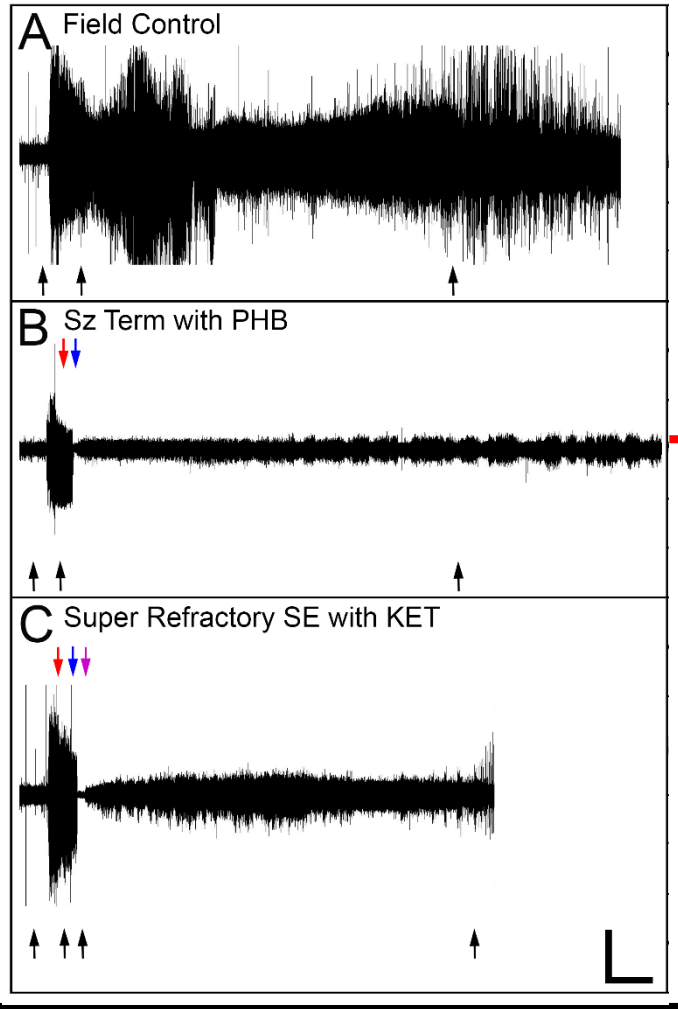
Standard Treatment Protocol Outcomes

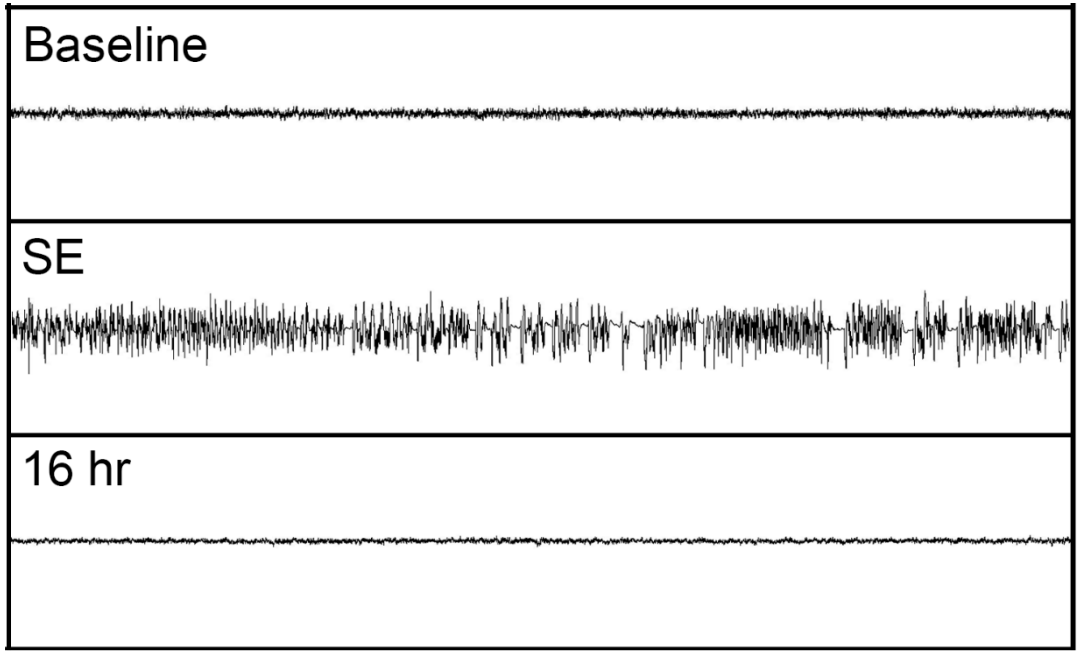




Morgan, et al., *Frontiers in Neuroscience* 2021

Standard Treatment Protocol Outcomes





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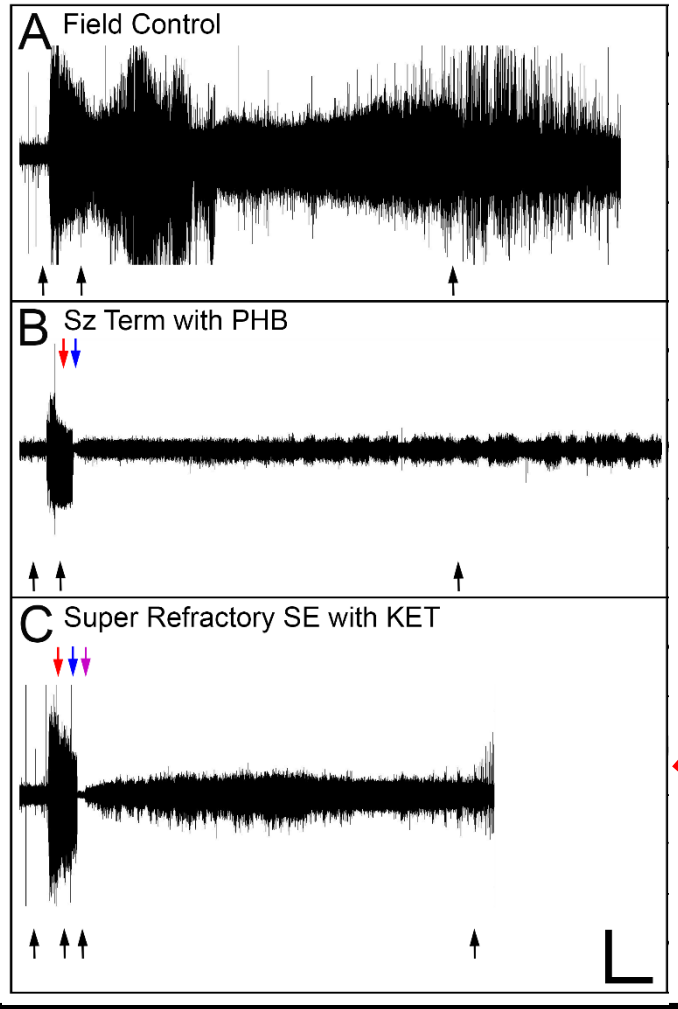

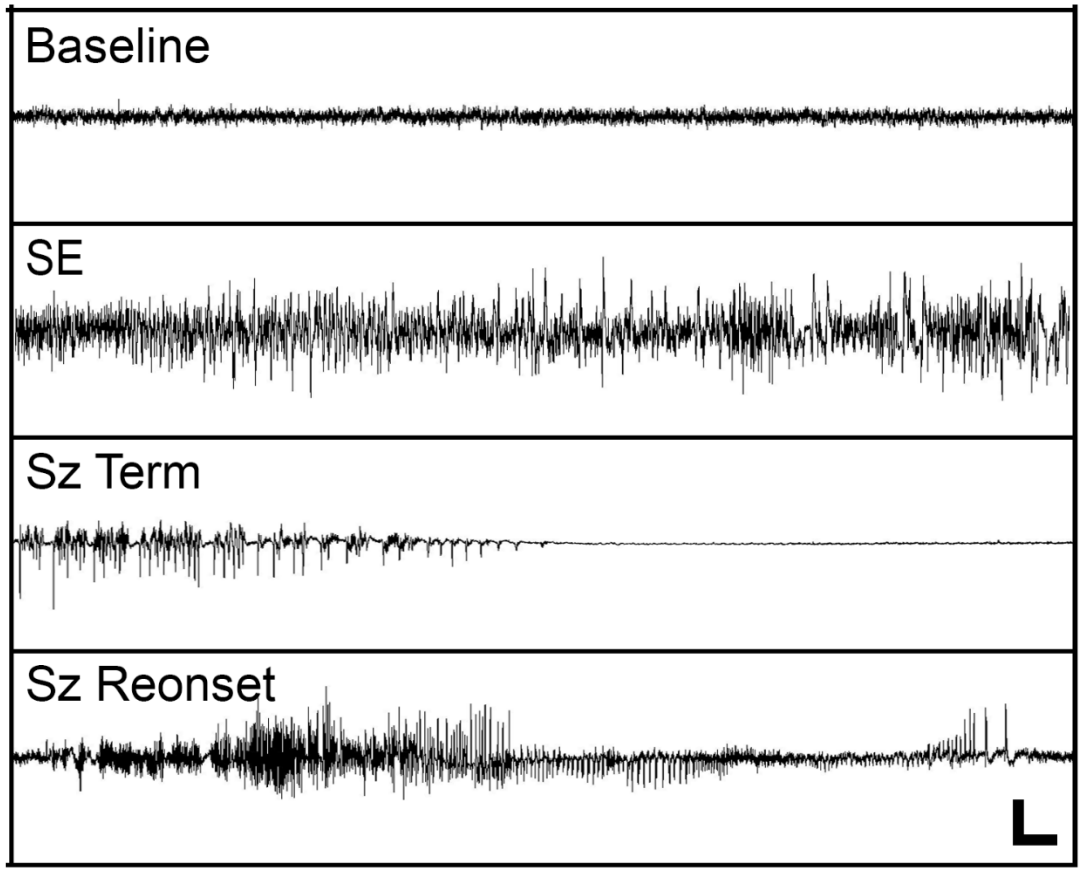

Morgan, et al., *Frontiers in Neuroscience* 2021

Summary & Discussion

- Nerve agent-induced SE progresses to SRSE in rats
  - How do we formalize the model?
  - What is the model good for?
- Not all second-line treatments are equal in this model
  - When does etiology matter?