Spreading Depolarizations: What are they and why do they matter for my patient?

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Disclosures

- No commercial or financial conflicts of interest.

- Deidentified clinical data are shown under IRB protocol 10-01760 for quality improvement and teaching purposes.

Objectives

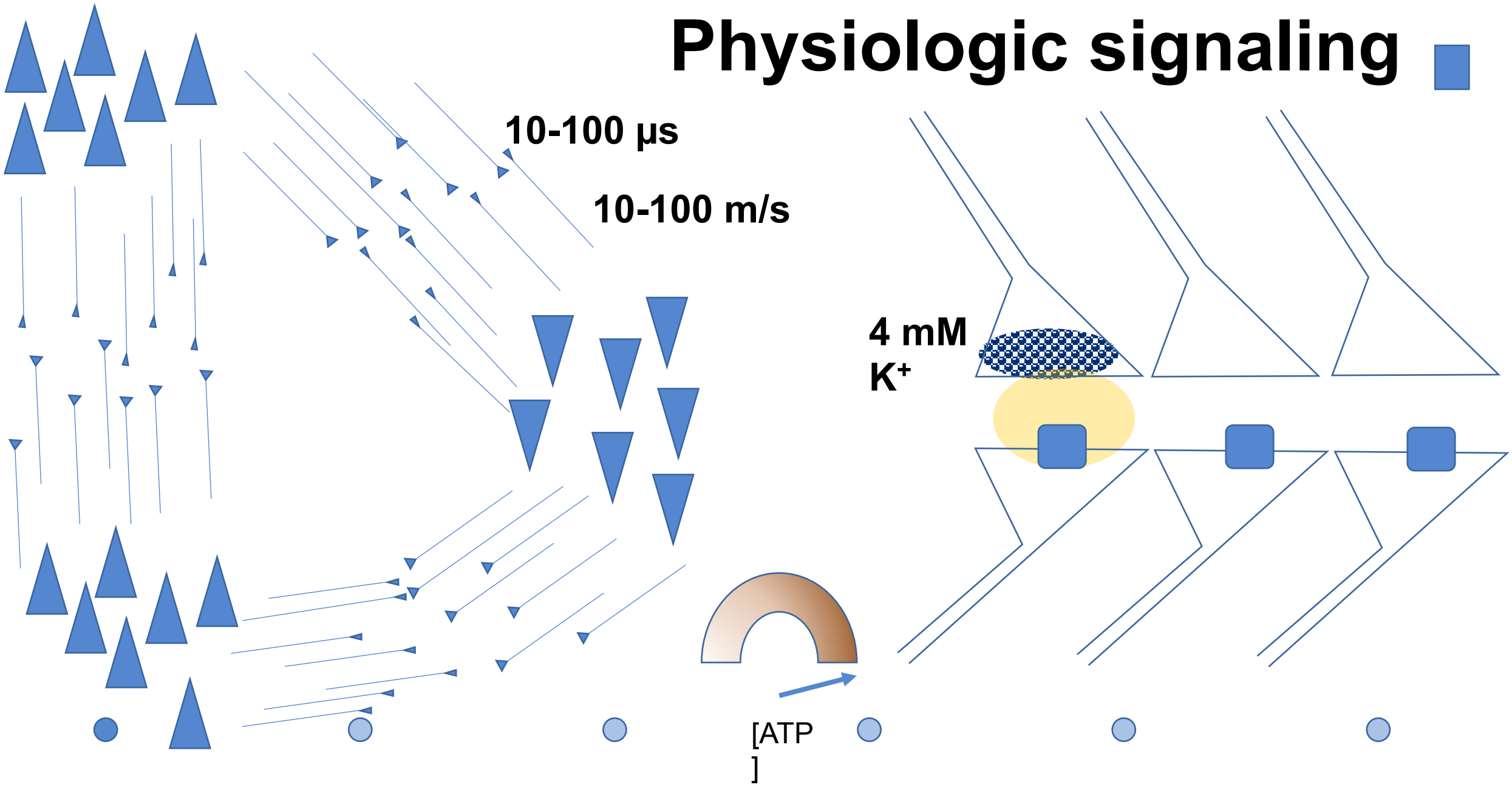
1) Compare and contrast spreading depolarization with synaptic signaling and seizure activity.

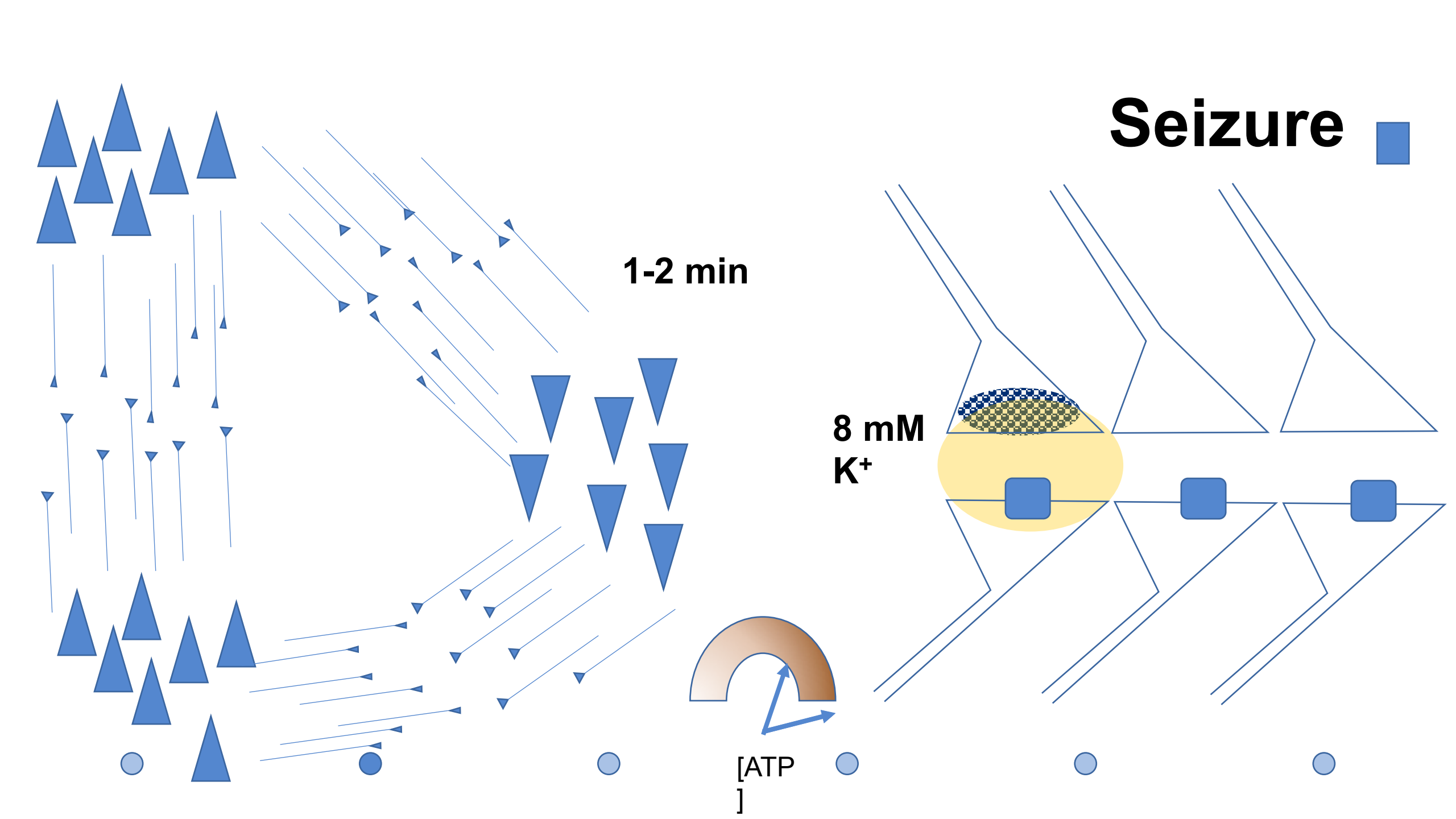
2) Recognize spreading depolarization as a feature of traumatic brain injury and a contributor to delayed lesion expansion.

3) Identify opportunities to detect and target spreading depolarizations to improve clinical practice.

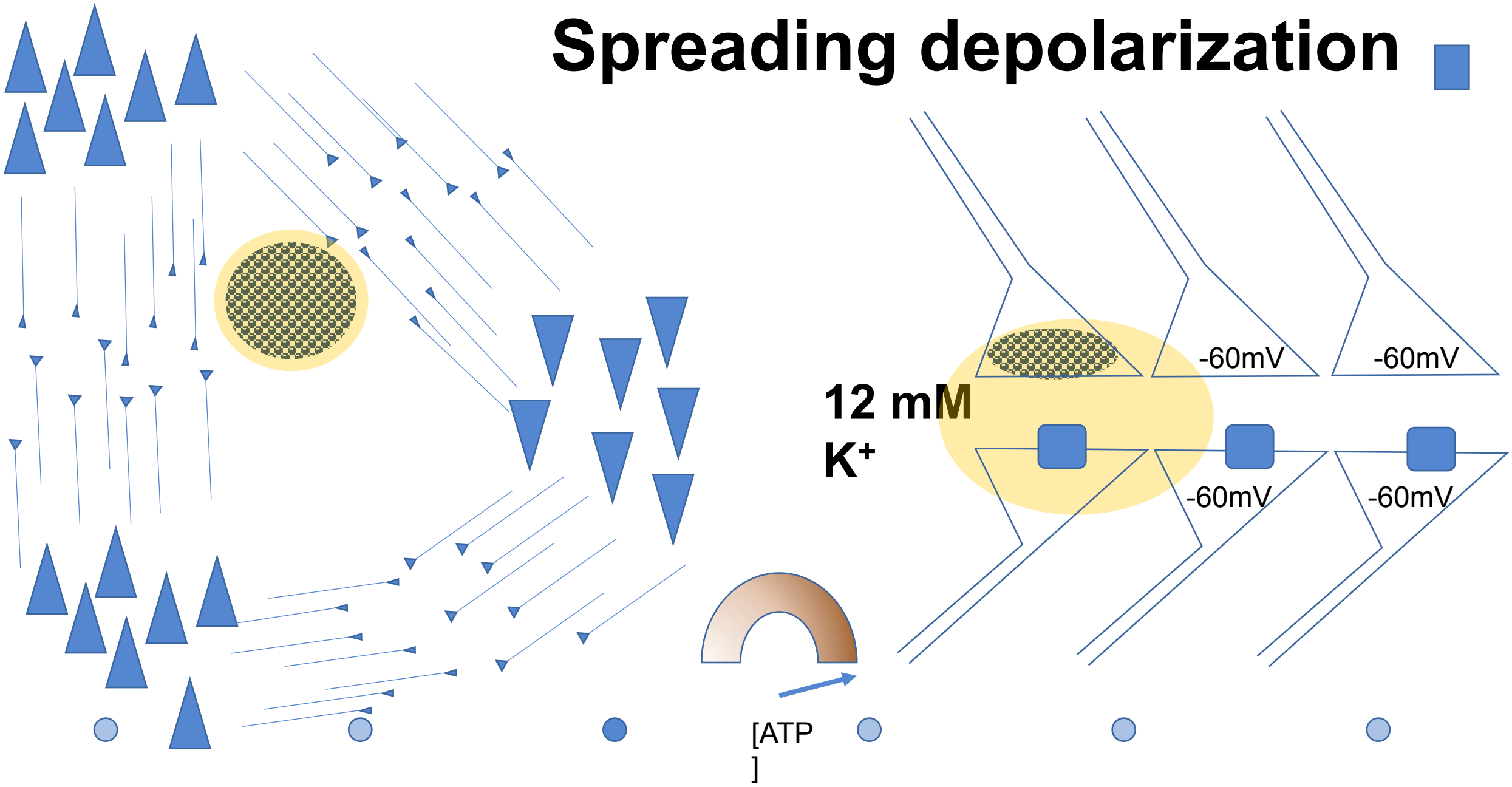
Compare and contrast spreading depolarization with synaptic signaling and seizure activity.

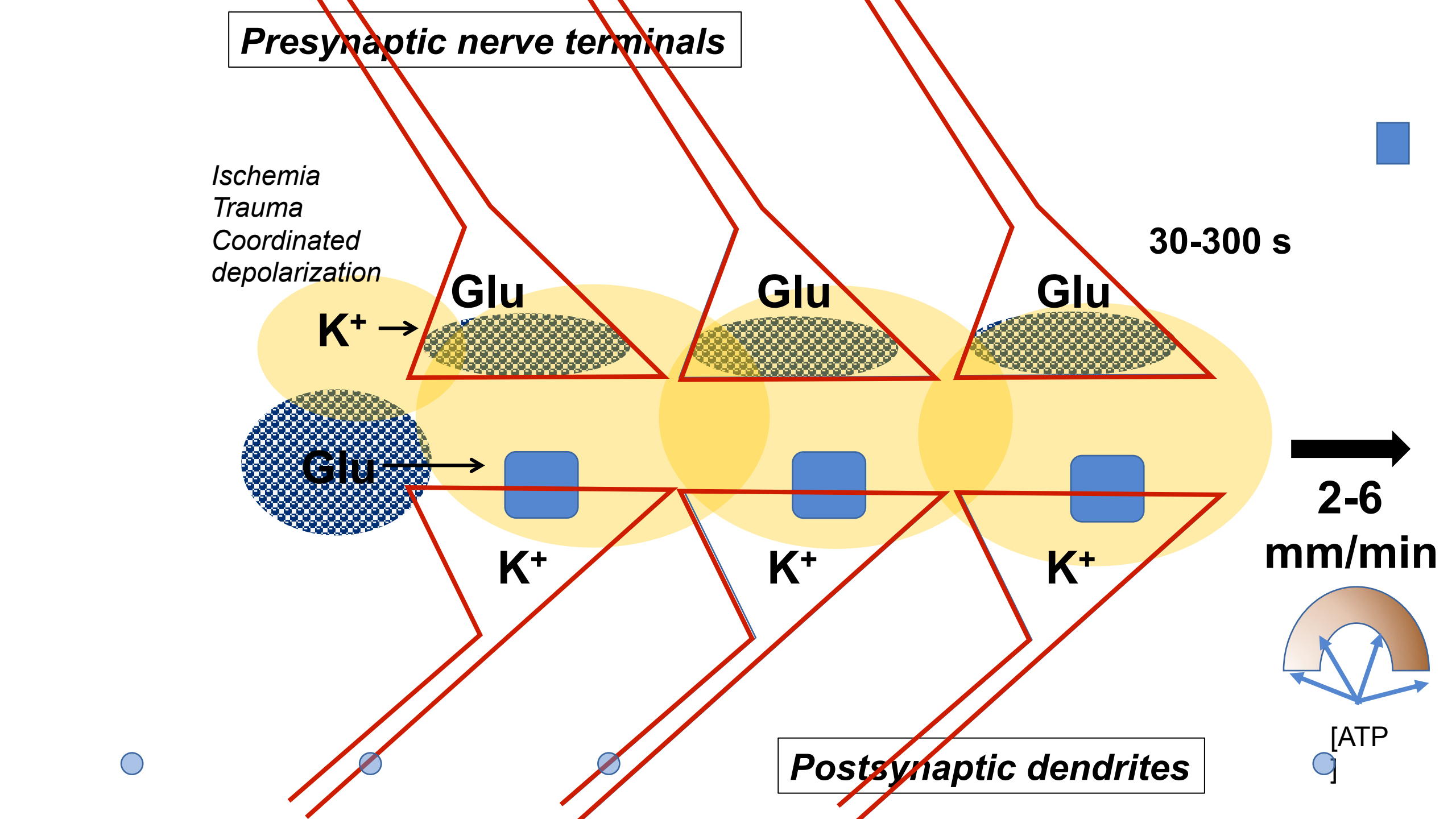
Physiologic signaling



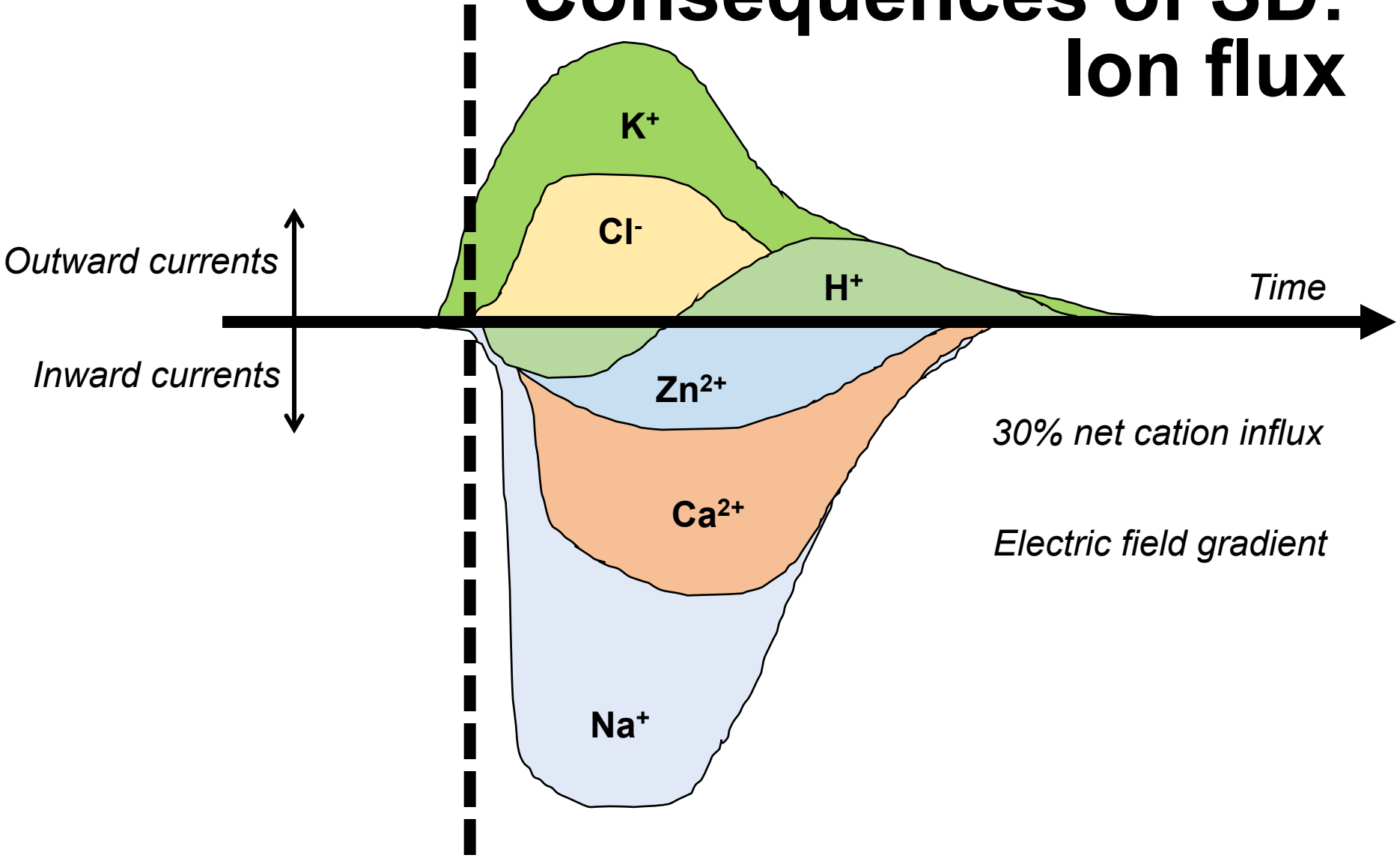

Seizure
1-2 min
8 mM
K+
[ATP
]

Spreading depolarization



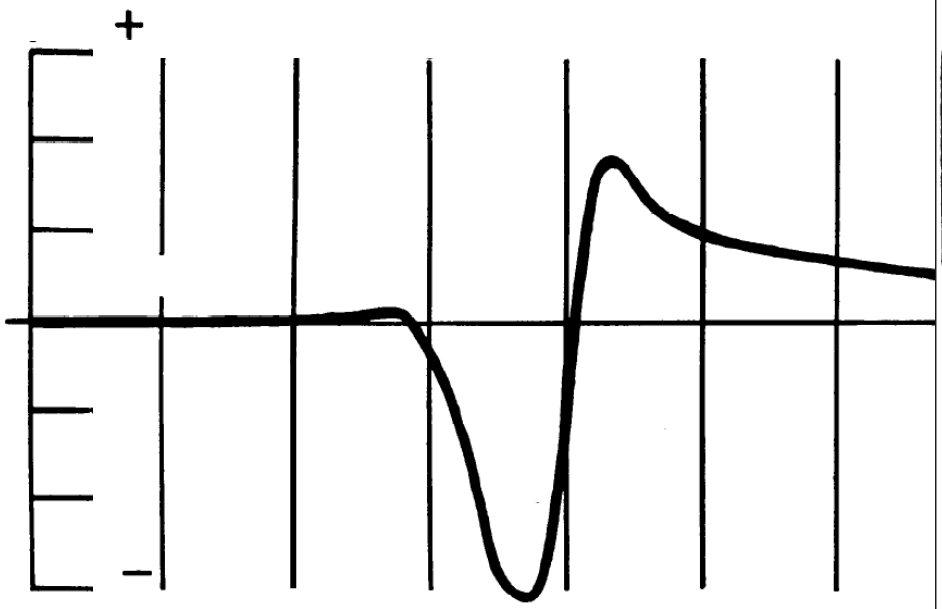

Presynaptic nerve terminals
Ischemia
Trauma
Coordinated
depolarization
30-300 s
Glu
Glu
Glu
K+
Glu
K+
K+
K+
2-6
mm/min
[ATP
Postsynaptic dendrites

Consequences of SD: Ion flux



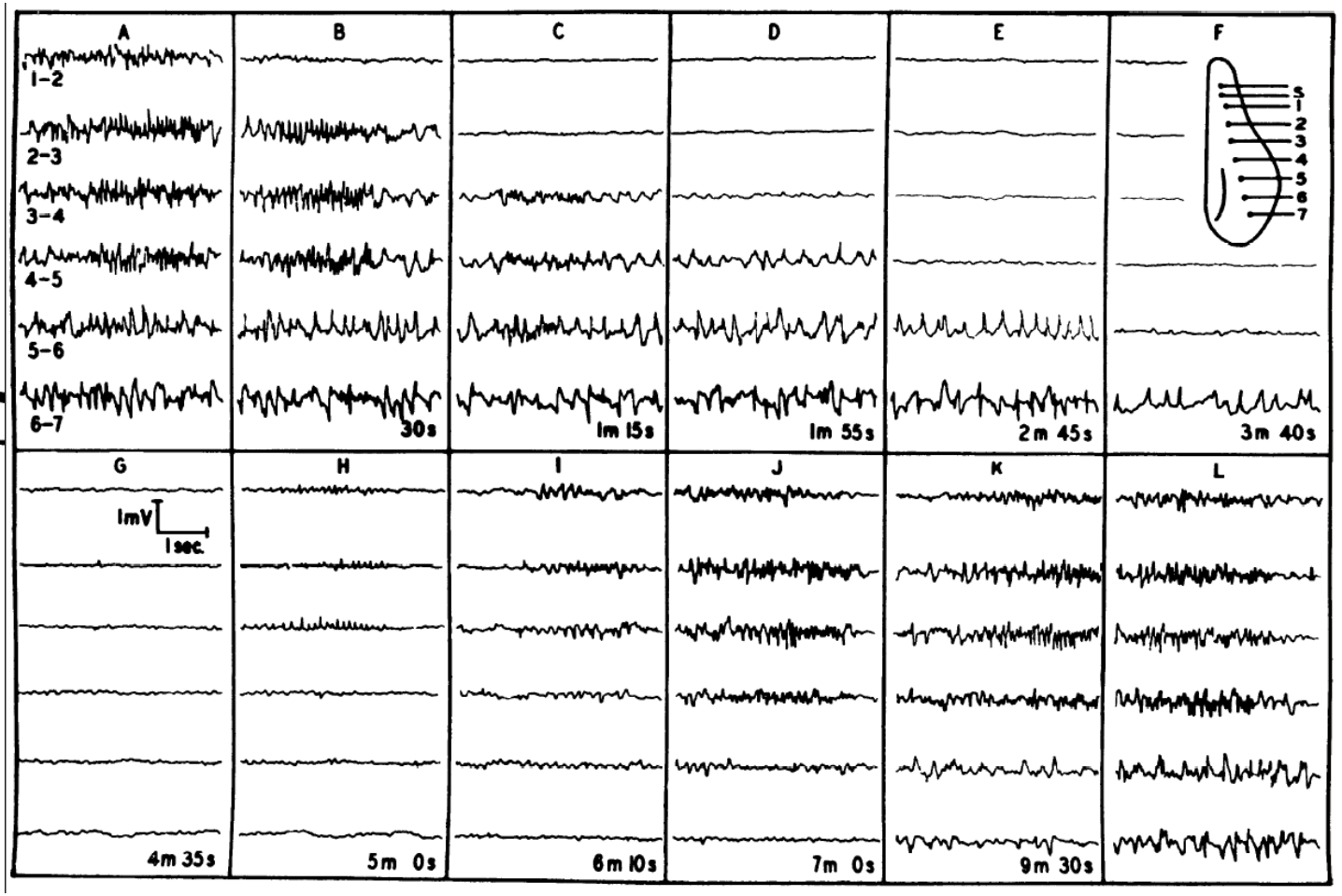
Consequences of SD

DC shift



AAP Leao, Journal of Neurophysiology 1947;10(6):409-14.

Depression of cortical activity

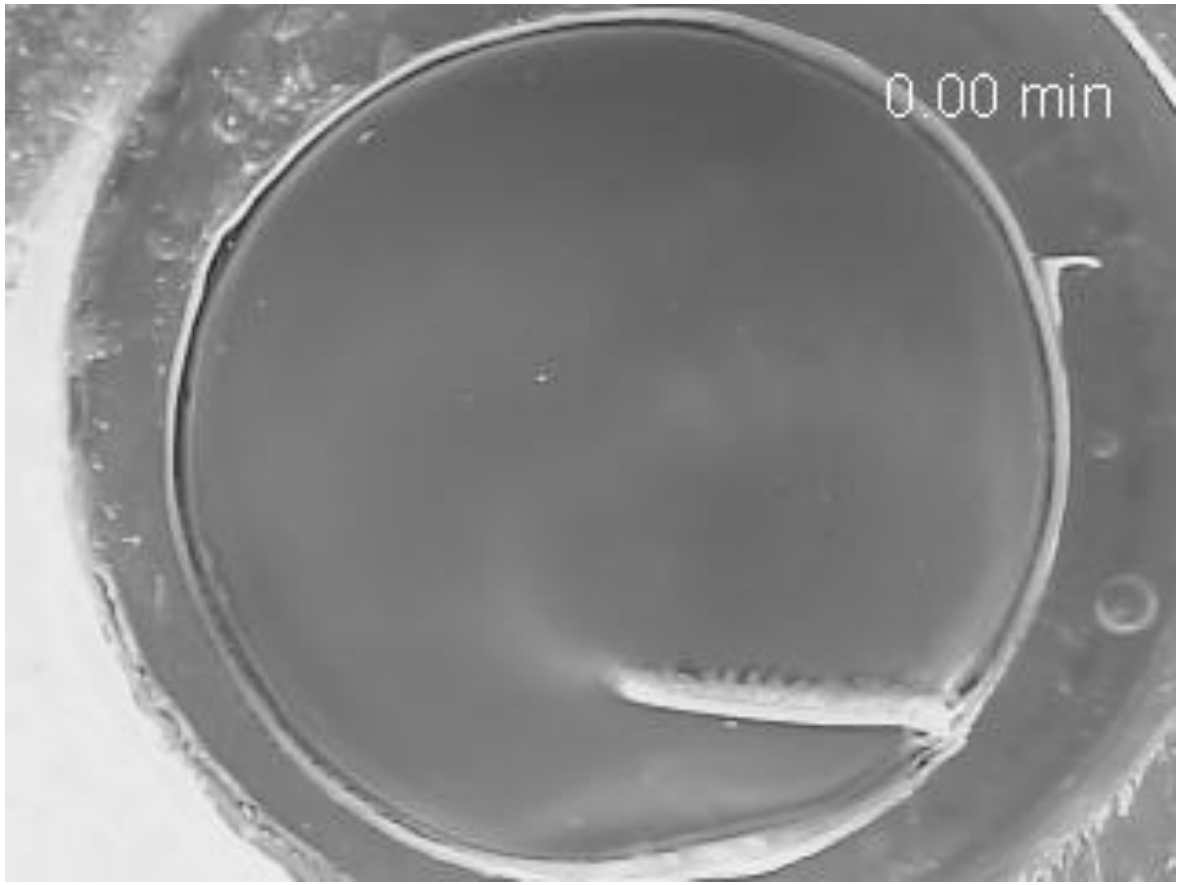


AAP Leao, Journal of Neurophysiology 1944a; 7:359-390.

Recognize spreading depolarization as a feature of traumatic brain injury and a contributor to delayed lesion expansion.

SD triggered mechanically

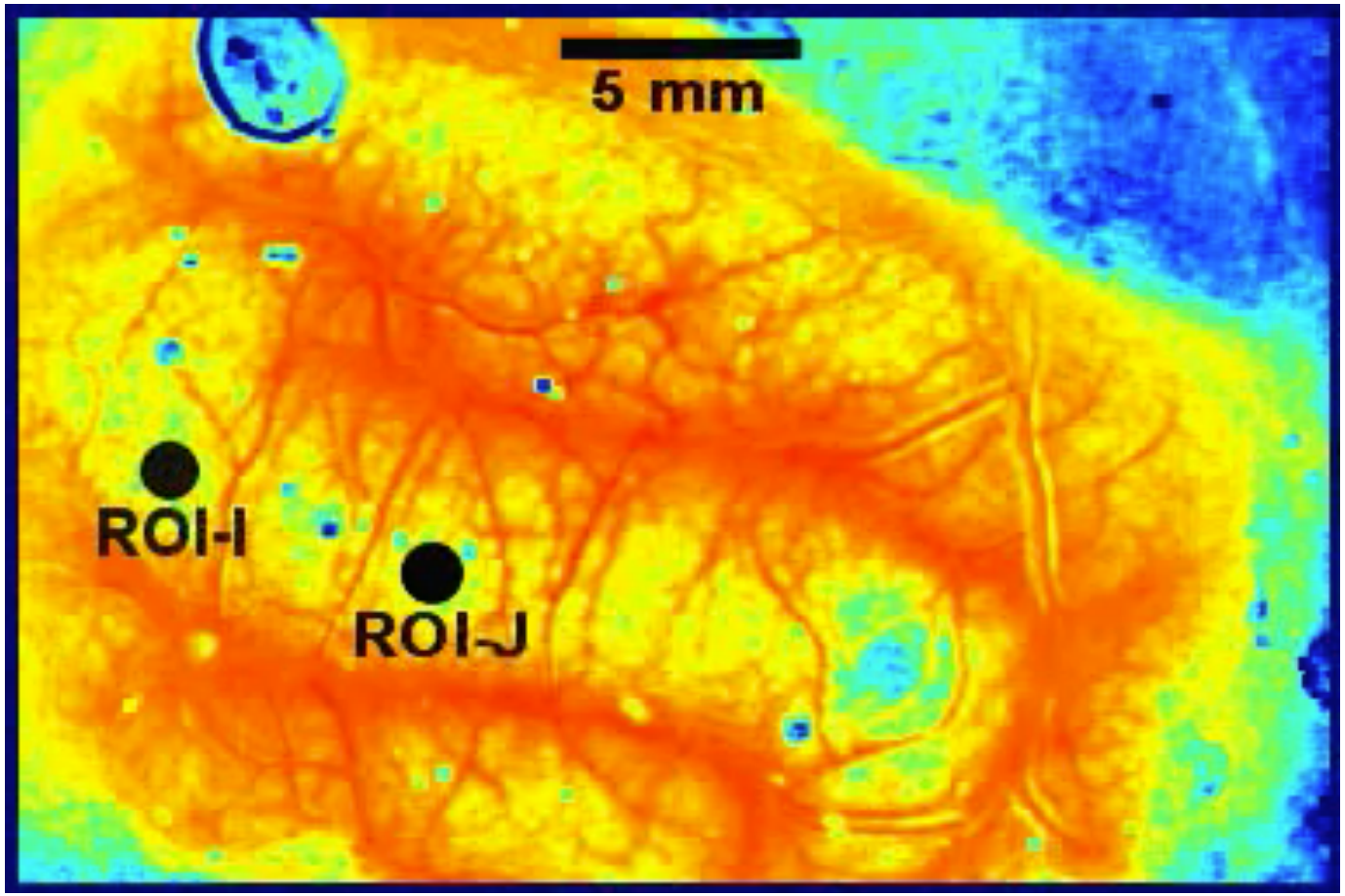
Chick retina



Yu et al 2009 PNAS

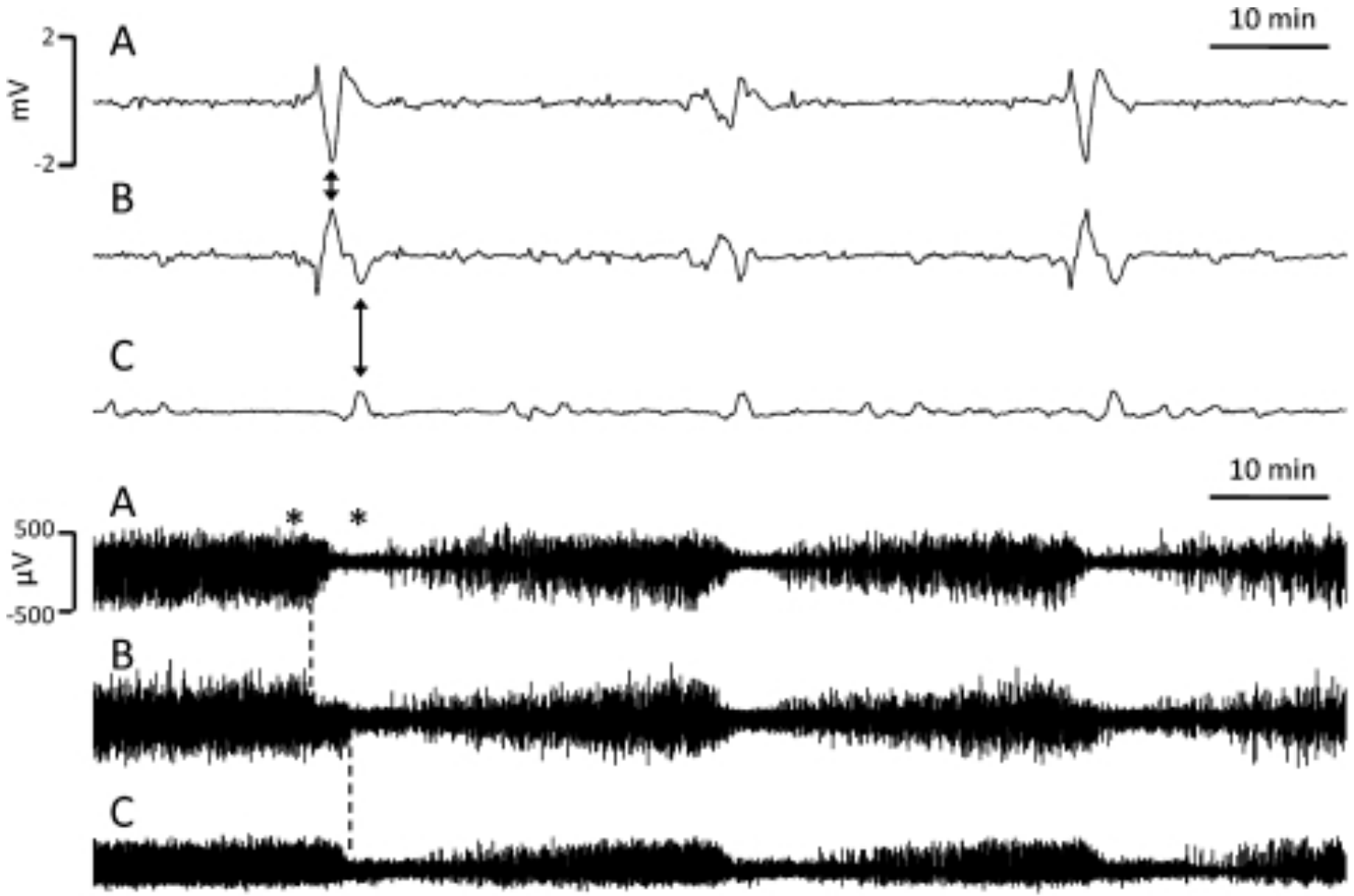
SD in metabolically heterogeneous tissue

Swine cortex



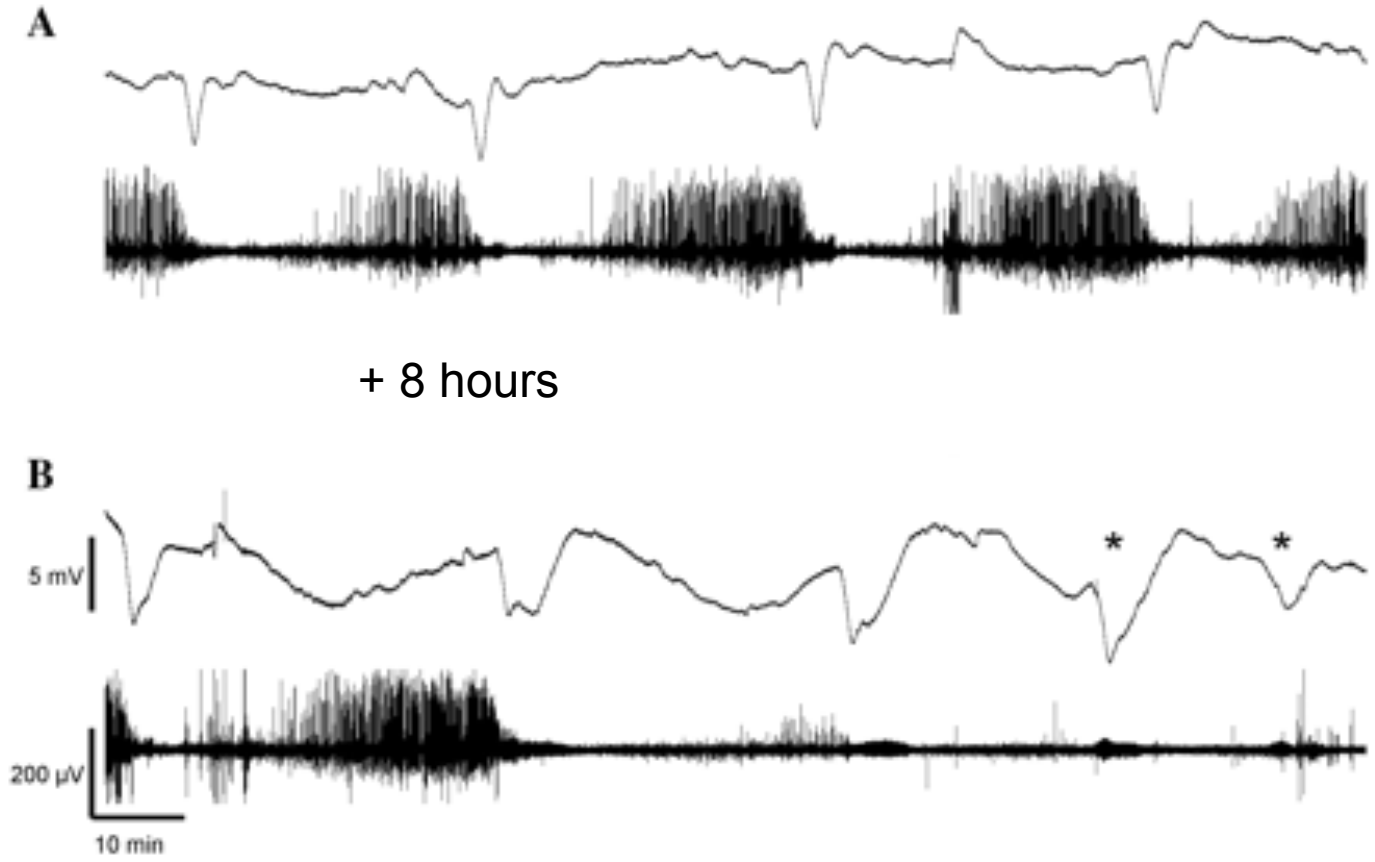
Strong AJ et al, Brain 130(4);2007:995-1008.

SD occurs in TBI



Hartings JA et al J Neurotrauma 2009 26(11):1857-1866.

SD associated with stepwise progression of injury



Hartings JA et al Brain 134(5):1529—540.

	Participants (n=103)
Age (years)	44 (30 to 60, 18 to 79)
Glasgow coma scale motor score*	
No response	24 (23%)
Extension	4 (4%)
Flexion	5 (5%)
Withdraws	18 (17%)
Localises	30 (29%)
Obeys	22 (21%)
Pupils*	
Both reacting	66 (64%)
One reacting	16 (16%)
Neither reacting	21 (20%)
Marshall CT category*	
Diffuse injury (2)	3 (3%)
Swelling (3)	4 (4%)
Shift (4)	3 (3%)
Evacuated mass lesion (5)	63 (62%)
Non-evacuated mass lesion (6)	29 (28%)
Traumatic subarachnoid haemorrhage	83 (81%)
Hypotension*	15 (15%)
Hypoxia*	19 (18%)
Prognostic score	0·1 (–0·5 to 1·2, –2·0 to 3·1)

Data are n (%) or median (IQR, range). *16 (1·9%) of the 824 covariate values were missing and were replaced by imputation, comprising four values for Glasgow coma scale motor score, one for pupillary reactivity, six for hypotension, four for hypoxia, and one for Marshall CT category.

***Table 2:* Covariates for outcome prediction**

	Common odds ratio (95% CI)	p
Prognostic score	1·76 (1·26–2·46)	0·0009
Depolarisation		0·0008
None	1·0	..
CSD	1·56 (0·72–3·37)	0·26
ISD	7·58 (2·64–21·8)	0·0002

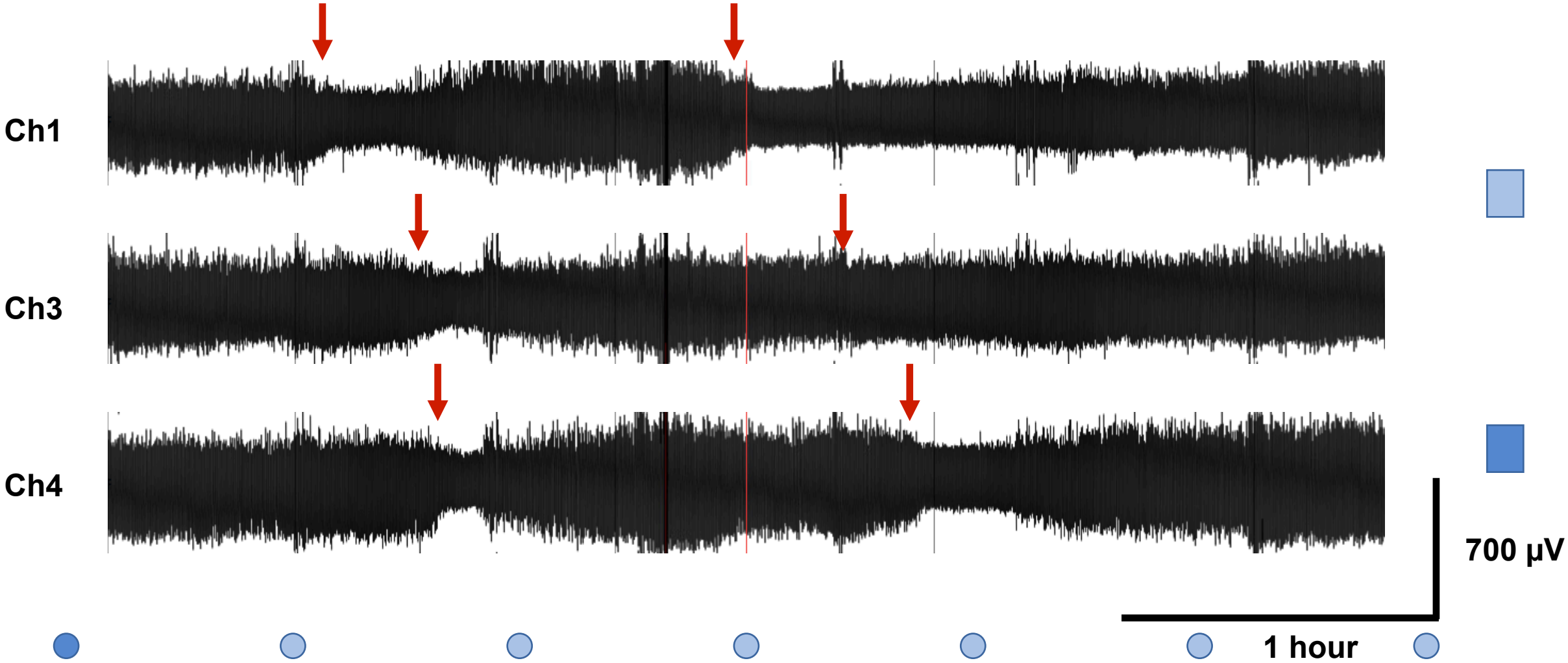
CSD=cortical spreading depression. ISD=isoelectric spreading depolarisation.

***Table 3:* Outcome prediction (multivariate ordinal regression analysis)**

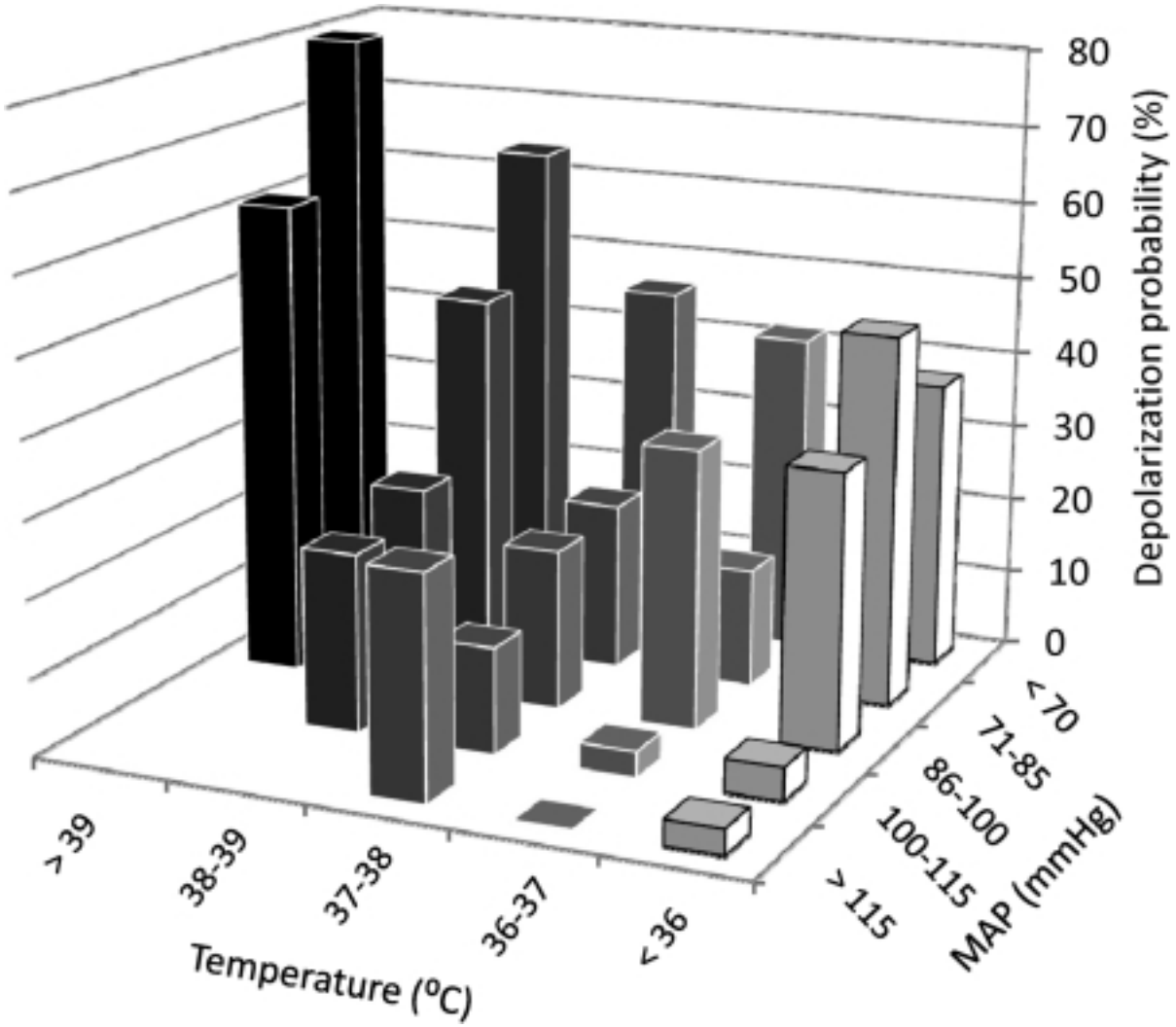
Hartings et al Lancet Neurol 2011

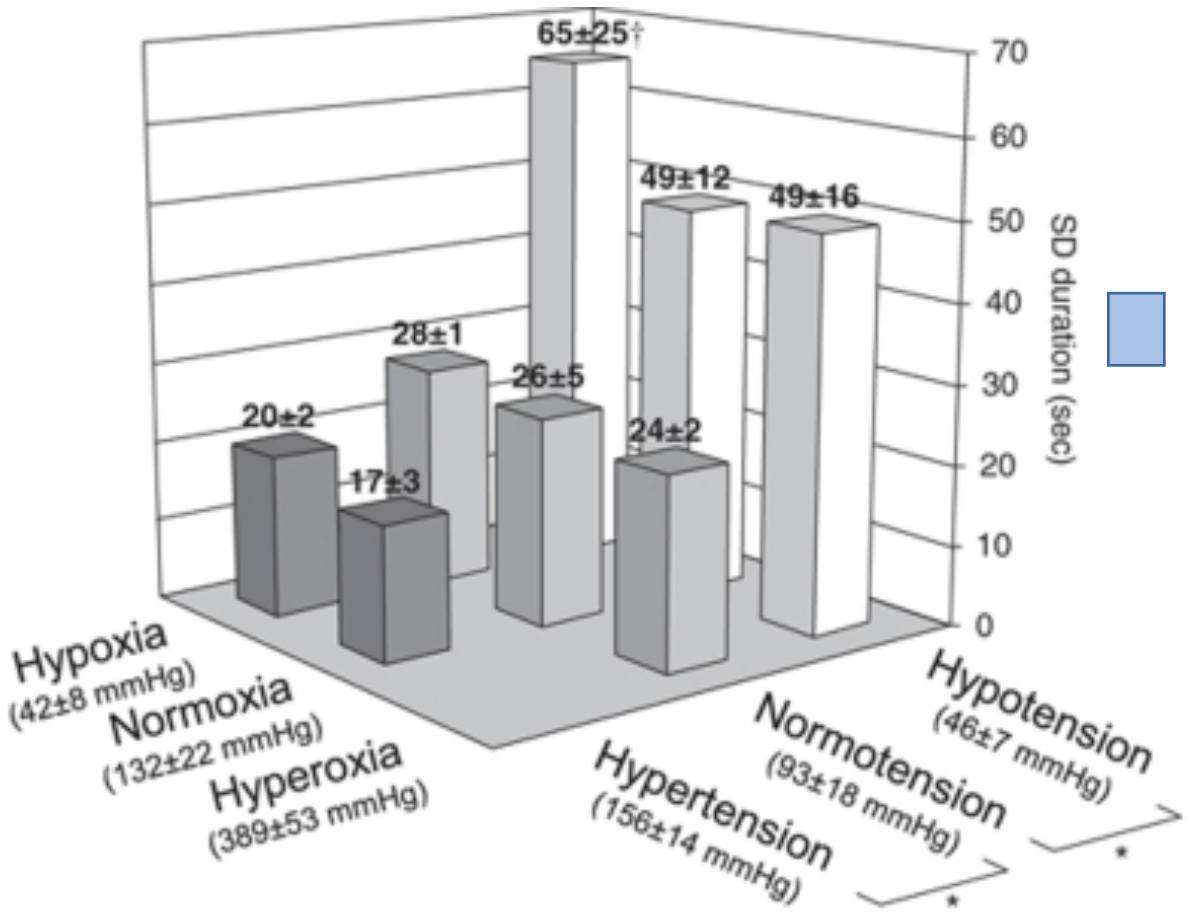
Identify opportunities to detect and target spreading depolarizations to improve clinical practice.

Recording and monitoring SD in standard clinical practice



Hypotension, hypoxia, and fever trigger SD

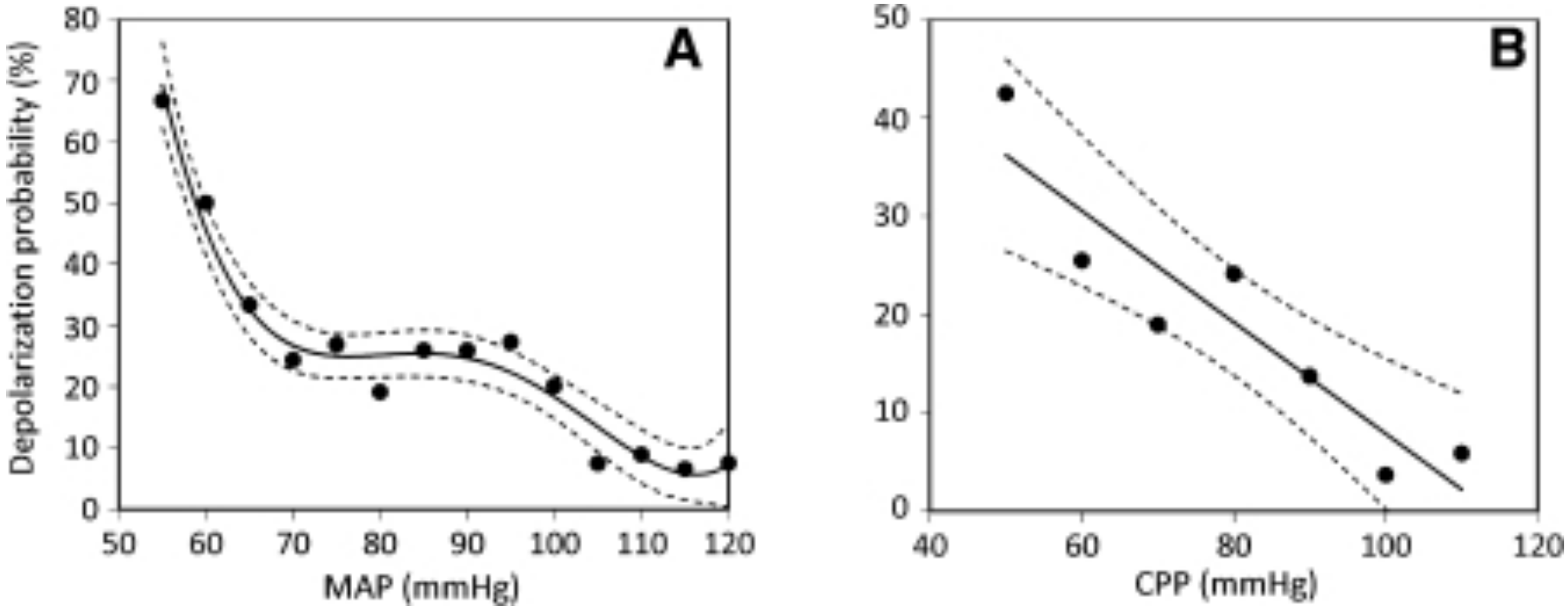




Hartings et al J Neurotrauma 2009

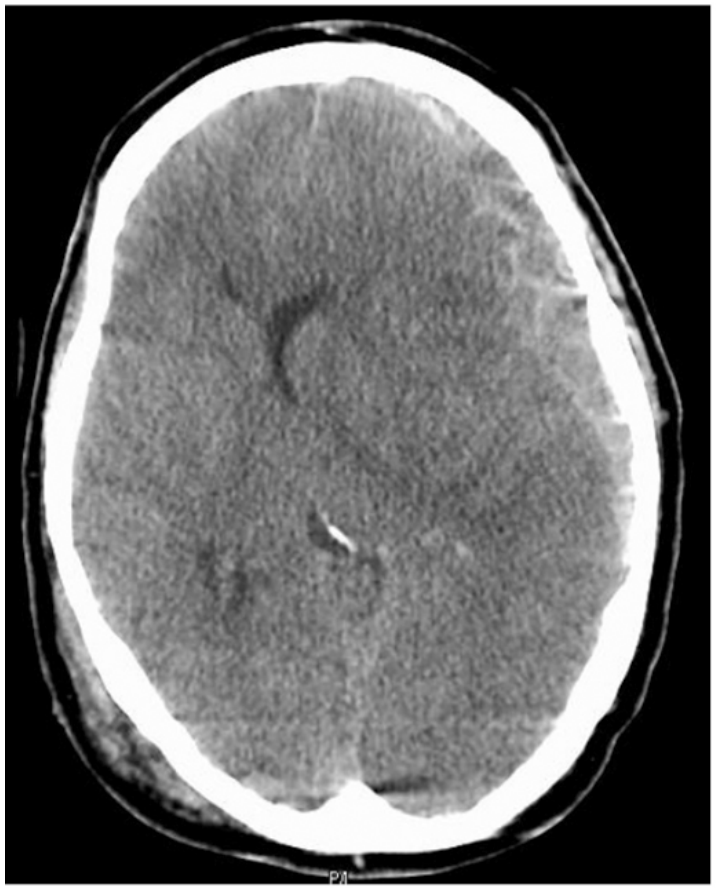
Sukhotinsky et al JCBFM 30(6);2010:1168-1177

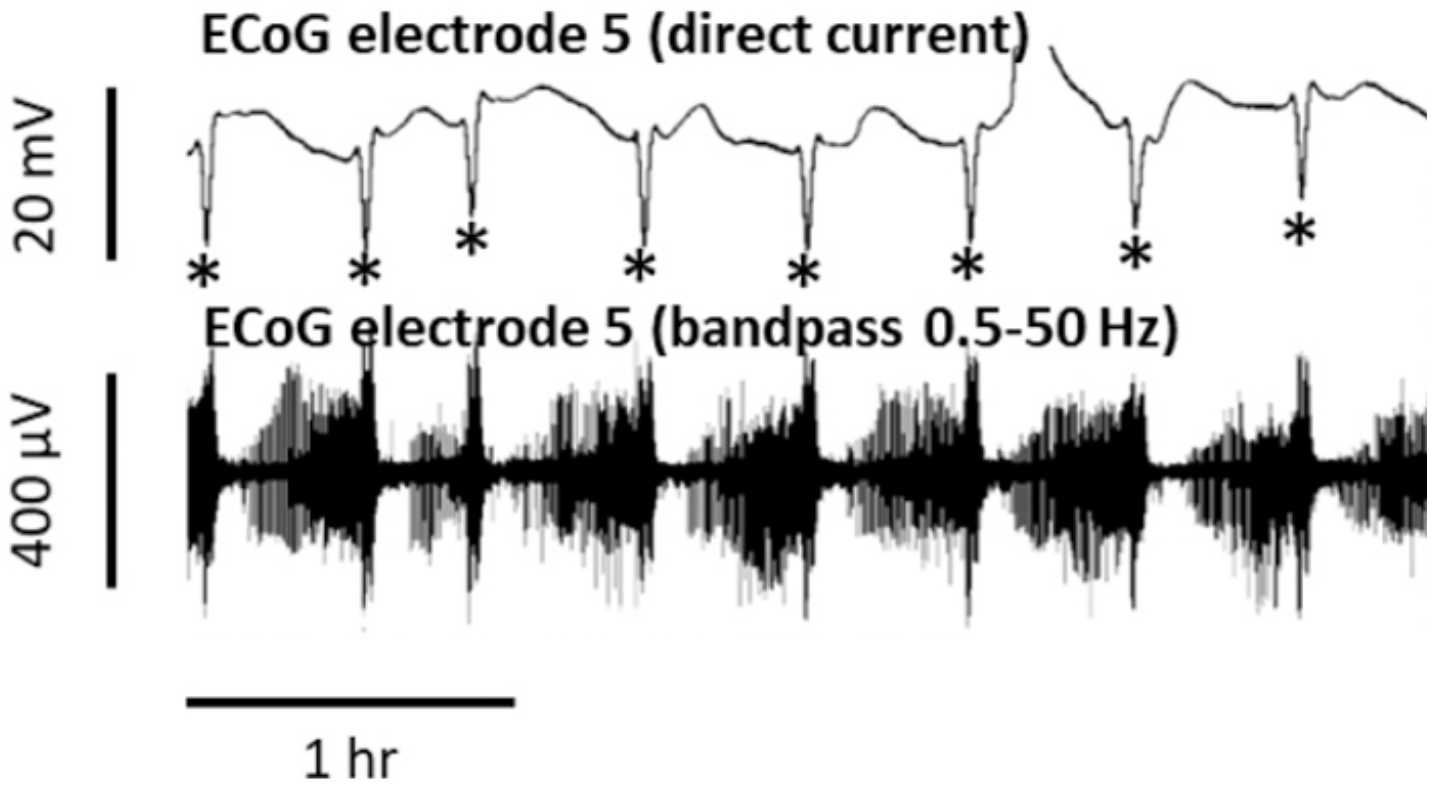
Cerebral perfusion pressure modulates SD



Hartings et al J Neurotrauma 2009

Ketamine inhibits SD





Hartings et al JNS 2018

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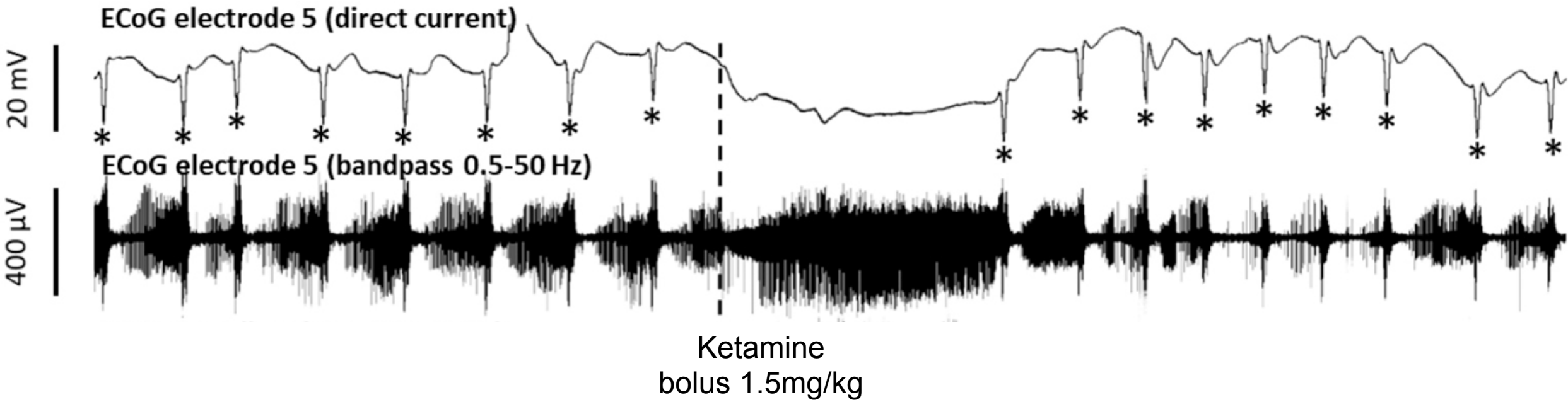

Hartings et al JNS 2018

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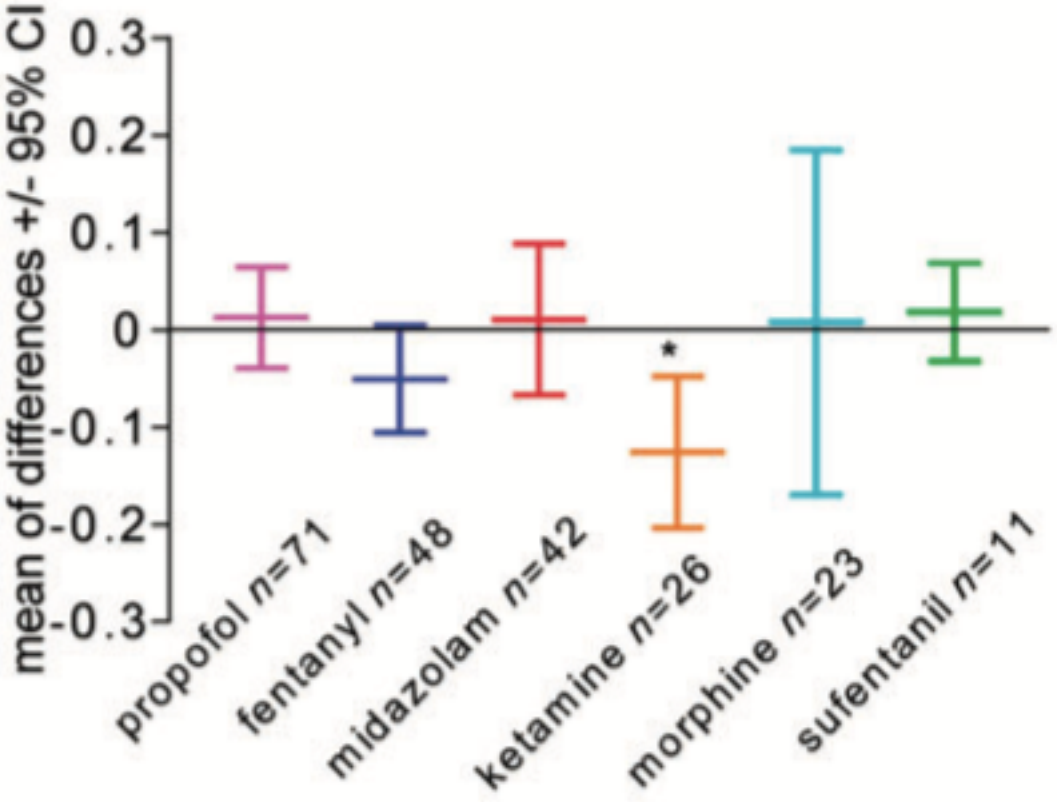
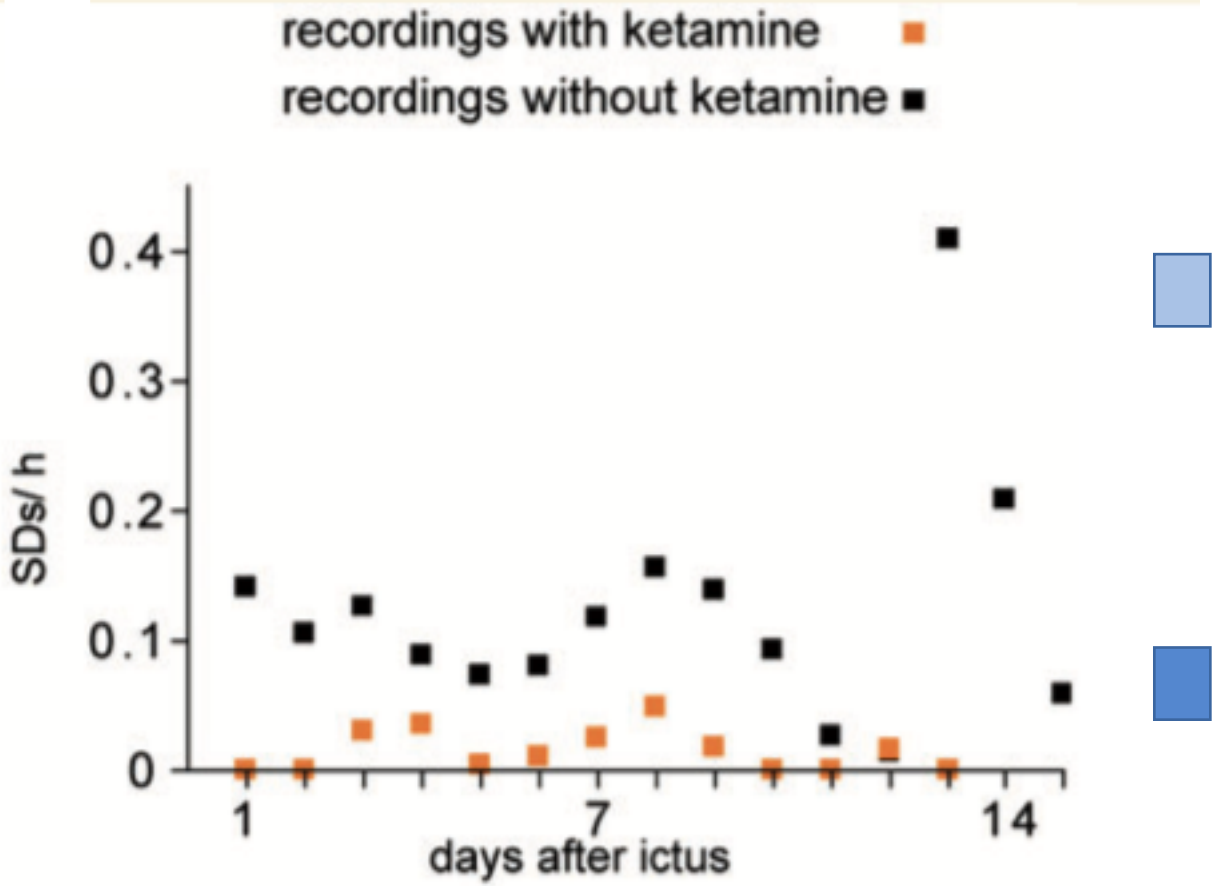




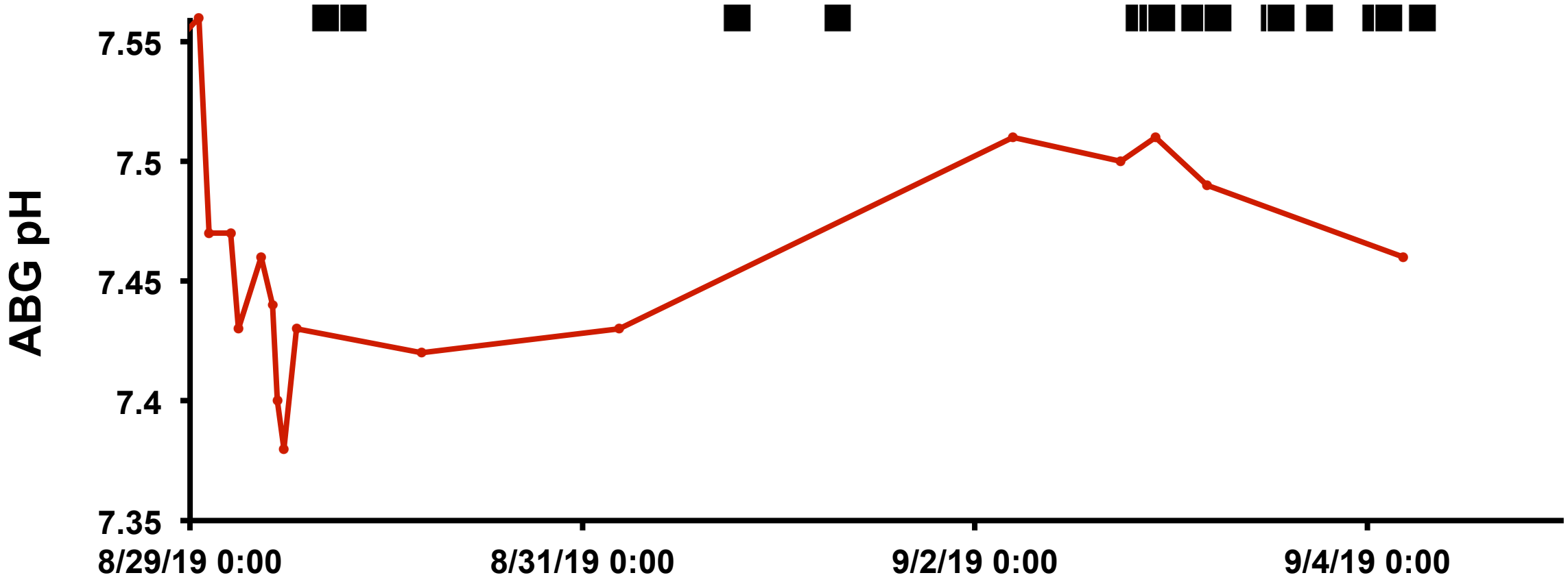
Hertle et al Brain 2012

Next steps:
Testable hypotheses from preclinical data

- Hypoxia and alkalosis should increase incidence of SD.

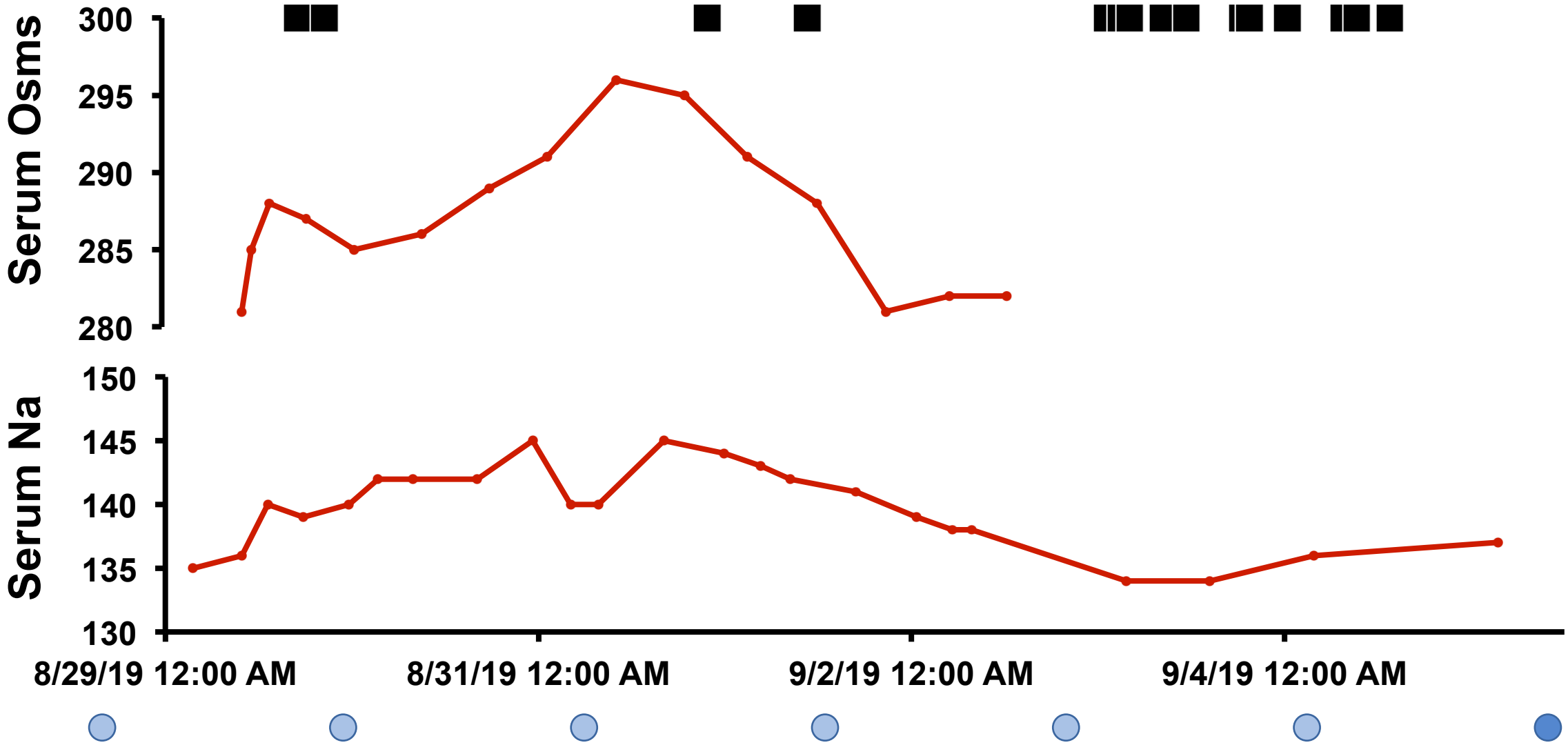
- Hyperosmolar therapies should decrease incidence of SD.

Is systemic alkalosis a risk factor for SD?



Unpublished data

Can hyperosmolar therapy prevent SD?



Unpublished data

Summary and Conclusions

SD is a profound, prolonged depolarization which propagates through grey matter via feed-forward release of excitatory neurotransmitters and potassium.

SD is a feature of traumatic brain injury, and contributes to secondary injury in the days following initial insult.

SD incidence and characteristics are affected by physiologic parameters within our control in the ICU environment. More research is needed to determine best practices.

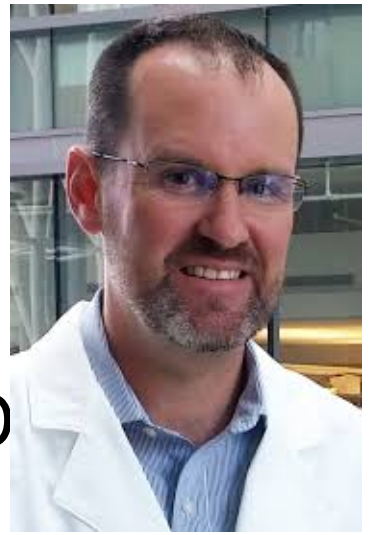
For more information

- COSBID.org
- braintsunamis.com

- britta.lindquist@ucsf.edu

Next steps:
Noninvasive detection and real-time SD alarms

- SDII substudy within TRACK-TBI.
  - Scalp EEG vs subdural ECoG recordings.



Jed Hartings

- Real-time bedside alarm and risk-stratification of SD
  - Moberg module in beta testing.

Sharon Jewell

Spreading depolarization is carried by:

A. Glia
B. Neurons
C. Blood vessels
D. Potassium
E. Glutamate
F. Gap junctions
G. NMDA receptors
H. Calcium

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  B. Neurons
  C. Blood vessels
  D. Potassium
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  H. Calcium

- If possible, SD should be suppressed in brain injury patients
  A. Yes
  B. No
  C. Show me outcome data

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  B. No
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- Sick injured brain is prone to SD. The proximate trigger for any given SD might be:
  A. Hypotension
  B. Fever
  C. Touching the patient
  D. Elevated ICP
  E. Vasospasm
  F. Seizure activity
  G. Hyponatremia/electrolyte disturbance
  H. Hyper/hypoventilation
  I. Hypoxemia

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- If I have an acute brain injury, give me:
  A. Intracranial monitoring and goal-directed therapy
  B. Hypertension, hypervolemia, hemodilution
  C. Anticonvulsants
  D. Pressors
  E. Ketamine
  F. Hypernatremia
  G. Targeted temperature management

- If I have an acute brain injury, give me:
  A. Intracranial ECoG monitoring and goal-directed therapy
  B. Hypertension, hypervolemia, hemodilution
  C. Anticonvulsants
  D. * Pressors – targeting CPP > ??
  E. * Ketamine – targeting malignant patterns (iSD, clusters) in real time
  F. Hypernatremia
  G. Targeted temperature management -- euthermia

- If I have an acute brain injury, give me:
  A. Intracranial monitoring and goal-directed therapy
  B. CPP (until it hurts)
  C. Real time SD alarms and responsive ketamine bolus