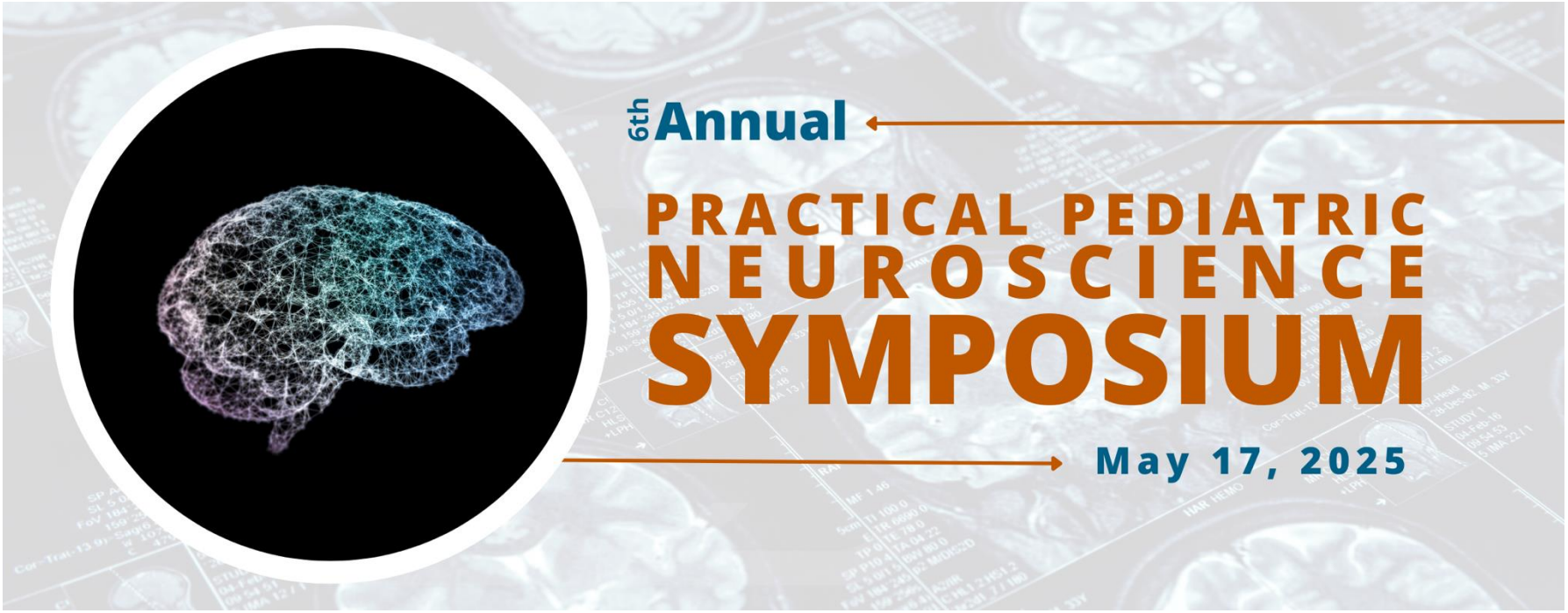

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Neuromodulation for Epilepsy Treatment

Chelsey Ortman, MD

Assistant Professor, Pediatric Neurology and Pediatric Epilepsy
The University of Texas at Austin, Dell Children's Medical Center

6th Annual Pediatric Neuroscience Symposium
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Interprofessional Continuing Education

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Chelsey Ortman, MD

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A commercial interest is any entity producing marketing, re-selling, or distributed health care good and services consumed by, or used on, patients.

Outline

- Drug-resistant epilepsy (DRE) and neuromodulation
- Discuss the evidence, limitations, and advantages of neuromodulation:
  - Vagus nerve stimulation (VNS)
  - Deep brain stimulation (DBS)
  - Responsive neurostimulation (RNS)
- Case study

Drug-resistant epilepsy (DRE)

- When seizures continue despite trials of at least 2 antiseizure medications (ASMs)
  - Caveat: ASMs appropriately chosen and adequately dosed
- Epilepsy affects ~470,000 children in the United States
- DRE affects 1/3 of those children

Zack, et al. MMWR Morb Mortal Wkly Rep. 2017

Drug-resistant epilepsy (DRE)

- Goals of treatment in DRE include:
  - Seizure control
    - Reducing risk of sudden unexplained death in epilepsy (SUDEP)
    - Preventing seizure-related injuries and hospitalizations
  - Improved quality of life
    - Ameliorating ASM side effects
    - Improving depression, anxiety, and psychosocial detriment
    - Allowing for developmental progression

Drug-resistant epilepsy (DRE)

- Surgical treatments can be helpful in DRE:
  - Targeted resection or ablation
  - Corpus callosotomy
  - Neuromodulation
- Strongly consider ketogenic diet trial
- In DRE, <24% likelihood an additional ASM will fully control seizures

Chen, et al. JAMA Neurol. 2018

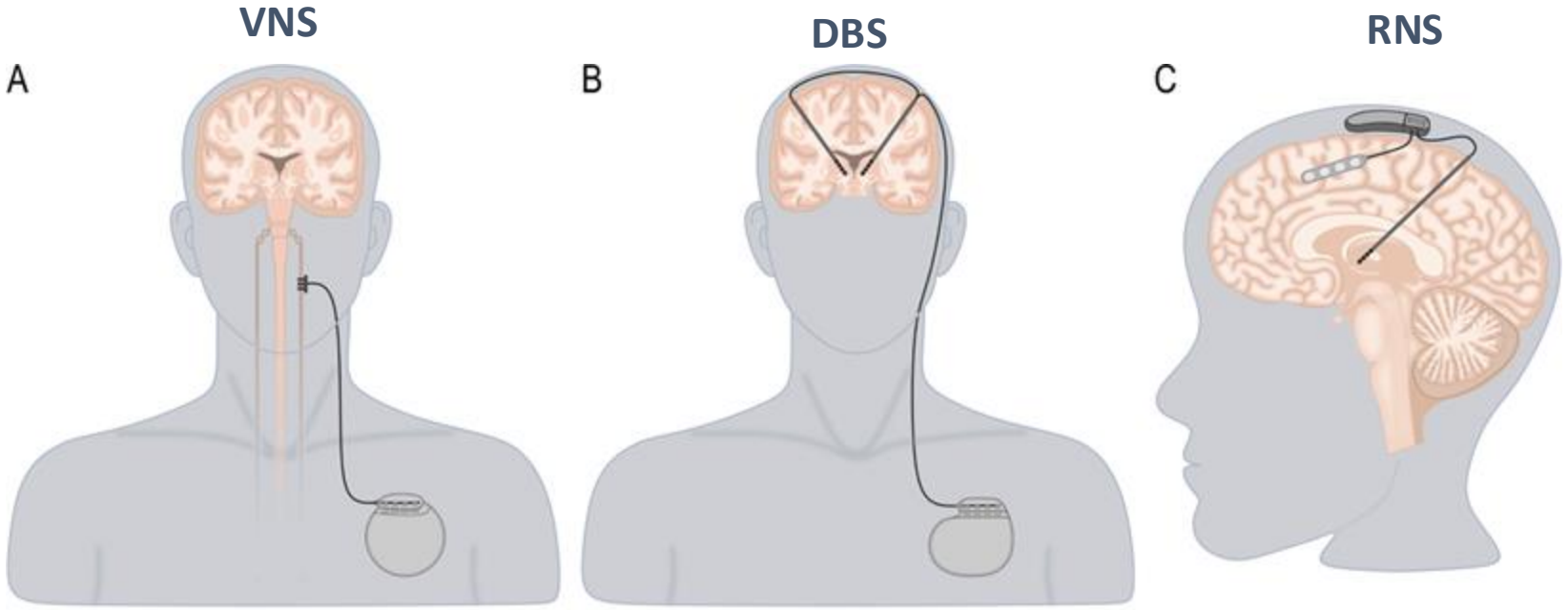
What is neuromodulation?

- Technology that impacts nervous system activity
  - Implanted and non-implanted devices
  - Electrical, chemical, or other agents
  - **Reversibly** modifies neuronal activity

What is neuromodulation?

- Highly targeted to specific areas
  - **Vagus nerve stimulation (VNS)**: left vagus nerve (CN X) → modulates thalamocortical circuits (theoretically)
  - **Deep brain stimulation (DBS):** anterior nucleus (ANT) or centromedian nucleus (CMN) of the thalamus
  - **Responsive neurostimulator (RNS):** can be placed throughout the cortex and/or in thalamic nuclei

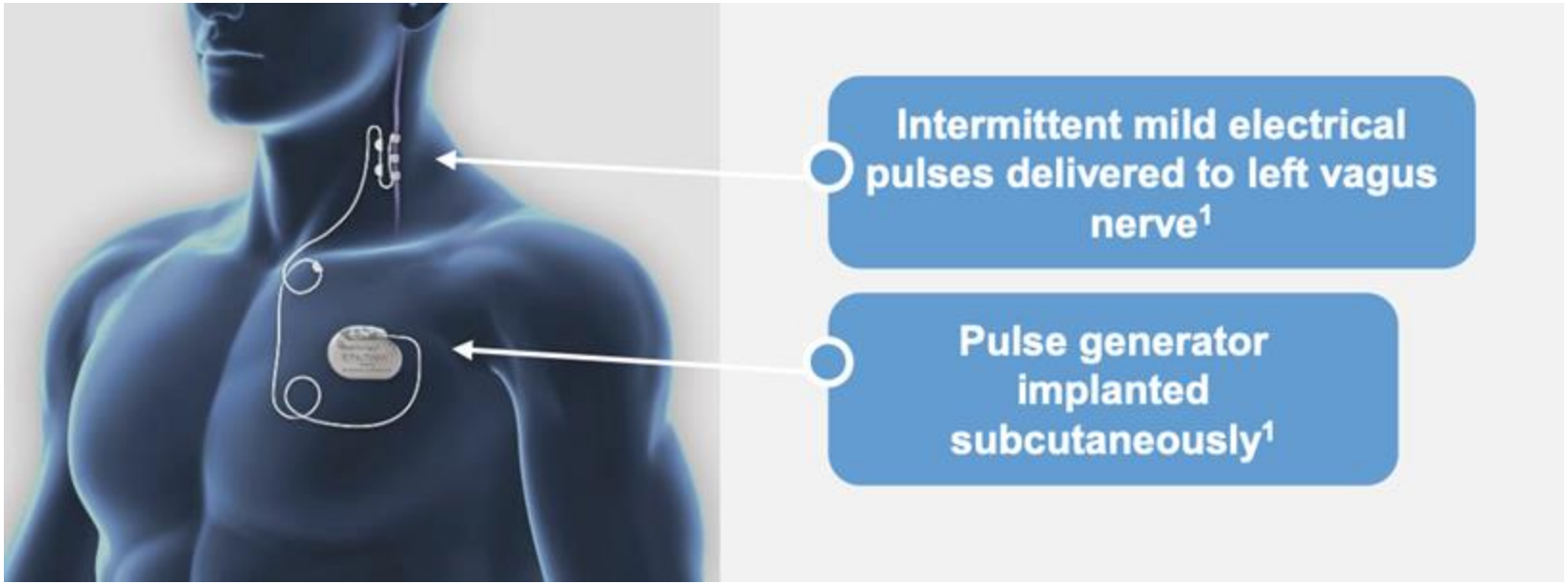
What is neuromodulation?



Gouveia, et al. Neurotherapeutics 2024

VNS

Vagus nerve stimulation



Above image used courtesy of Liva Nova.

1. VNS Therapy ™ System Patient's Guide for Epilepsy. LivaNova USA, Inc.; 2022.
2. Wheless, et al. Epilepsy Behav. 2018

VNS indications for epilepsy

- FDA: patients > 4 years with drug-resistant epilepsy (continued seizures with at least 2 appropriately chosen antiseizure medications)
- Seizure focus unclear or in eloquent cortex
- Patient input

VNS features

Open loop

Original use of VNS

Scheduled delivery of current (ex: stim on 30 s, off 5 min)

Closed loop

AutoStim (in last 15 years)

Activated by HR change

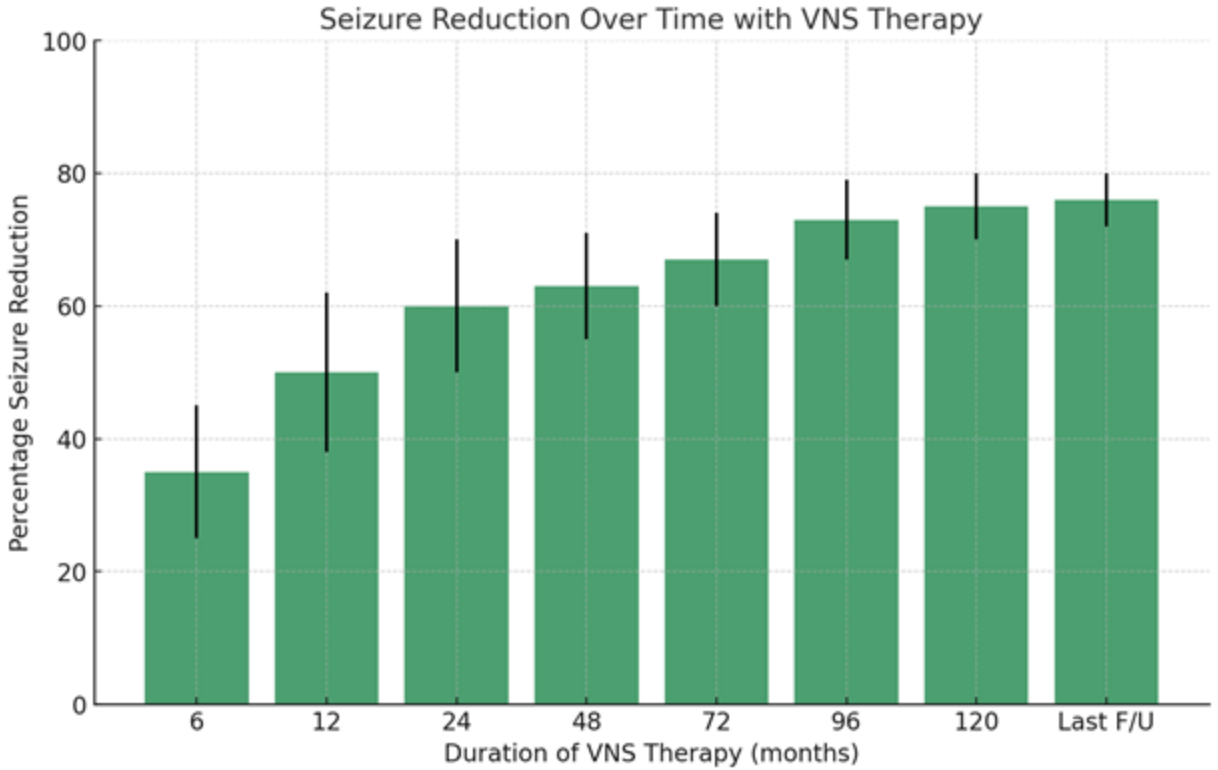
Shown to help decrease seizure severity, duration, frequency

Magnet

Manual activation of therapy
Typically with clinical events

Fisher, et al. Neuromodulation. 2016

VNS efficacy over time



Elliott, et al. Epilepsy Behav. 2011

Pooled analysis of VNS outcomes

- Systematic review and meta-analysis of 101 studies
- Pooled prevalence estimate for patients with ≥50% seizure reduction = 56%
- Pooled prevalence estimate for seizure freedom = 12%
- Association with better seizure outcomes w/VNS: fewer ASMs, older age

Jain, et al. Neurology. 2021

Contraindications and considerations

- Absolute:
  - Left vagotomy

- Relative / considerations:
  - Pregnancy (safety not established)
  - Active peptic ulcer disease
  - Insulin-dependent diabetes mellitus
  - Pre-existing swallowing, cardiac, or respiratory difficulties; smoking
  - May affect other implanted devices (i.e. pacers), requires careful programming
  - Underlying arrhythmias – postoperative bradycardia can occur

Potential adverse effects

- Most common: coughing, hoarseness, dyspnea, and headache – generally improve over time
- Sleep apnea (especially with higher current)
- Surgical: infection, Horner's syndrome, vocal cord paralysis
- Lead fracture, generator malfunction
- Need for battery replacement (typically 5-7 years)
- Rare: paresthesia, insomnia, nausea, ataxia, dyspepsia

DBS

FDA approved uses of DBS in epilepsy

Approved in **2018**

Open-loop stimulation of the bilateral anterior nucleus of the thalamus

Ages 18+ years (with ongoing pediatric studies)

For intractable focal epilepsy with or without secondary generalization

SANTÉ trial outcome

- For 110 implanted patients from 2004-2016
- At 7 years post-implant, median seizure frequency reduction from baseline was **75%** ($p<0.001$)
- Twenty patients (18%) reported seizure freedom at 7 years

Salanova, et al. Epilepsia. 2021

Reported adverse events at 5 years (SANTÉ trial)

Hardware-related in 22.7%:

- Paresthesia (18.2%)
- Implant site pain (23.6%)
- Implant site infection (12.7%)
- Electrode misplacement (8.2%)

Procedural-related in 4.5%:

- Asymptomatic intracerebral hematoma

Self-reported neuropsychological symptoms:

- Depression (32.7%)
- Memory impairment (27.3%)

Salanova, et al. Neurology. 2015

Advantages

- Non-lesional approach: approved for focal (ANT) and generalized (CMN) epilepsy
- Titration of stimulation parameters to maximize benefit and reduce adverse effects
- Promising preliminary data even in patients with prior VNS and resective surgery

Lozano, et al. Nat Rev Neurol. 2019

Disadvantages

- Currently requires invasive intracranial implantation of electrodes and extracranial implantation of stimulation generator
- Battery replacement (typically after 10-15 years, now with rechargeable model)

Lozano, et al. Nat Rev Neurol. 2019

RNS

Introduction to RNS

Responsive neurostimulation (RNS) was approved in 2013 for ages 18+ with drug-resistant focal epilepsy with 1-2 epileptogenic foci

RNS is a “closed-loop” system that continuously monitors electrical activity at the zone of implantation

RNS responds with electrical stimulation when epileptiform activity is detected, with detection parameters programmed by the clinician

Effectiveness

- Initial randomized, placebo-controlled, multicenter trial of 191 patients showed seizure reduction of 38% in stimulated group vs 17% in controls
- Median **53% seizure reduction** in stimulated patients at **2 years** and **48-66%** at **3-6 years** after implantation
- Location of seizure focus appears to be relevant:
  - 70% improvement in the frontal or parietal lobe
  - 58% in the temporal lobe
  - 51% with multi-lobar onset

Heck, et al. Epilepsia. 2014

Advantages

- Tailor implantation to targeted cortical/subcortical areas
- Long-term electrocorticography
  - Data for or against a proposed focal resection
  - Monitor response to medications
  - Understand seizure triggers and diurnal data

Disadvantages

- Requires intracranial placement of generator and leads, and often also requires prior invasive stereoelectroencephalography to pinpoint seizure focus
- Battery replacement (typically 7-10 years)
- Patients must remember to periodically upload data and come to clinic for adjustments

Complications

- Intracranial hemorrhage (< 5%), none with long-term sequelae)
- Infection risk (5%)
- Implant site pain (16%)
- Headache (11%)
- Uncomfortable sensation (dysesthesia) (6%)

Heck, et al. Epilepsia. 2014

Case example

- “Eli” is a 16-year-old male with mild intellectual disability and daily generalized tonic and generalized tonic-clonic (GTC) seizures associated with Lennox-Gastaut syndrome (LGS).
- He has prolonged tonic-clonic seizures lasting 20 minutes or more in times of illness.
- He has tried 8 different antiseizure medications without significant reduction in daily seizures.
- Eli’s family is interested in epilepsy surgery as a possible palliative treatment for his daily seizures.
- How would you advise the family about the potential options for neuromodulation?

Case example

- Eli undergoes VNS placement, complicated by slight hoarseness at 1 year post-placement, which is alleviated by reducing the current of stimulation in clinic.
- He has approximately 50% reduction in the frequency of GTC seizures and 40% reduction in the frequency of tonic seizures at 2 years post-placement, but he continues to have occasional episodes of prolonged GTCs over 20 minutes when he is ill.
- His family is wondering if there are any other surgical therapies that might be available as he reaches adulthood.

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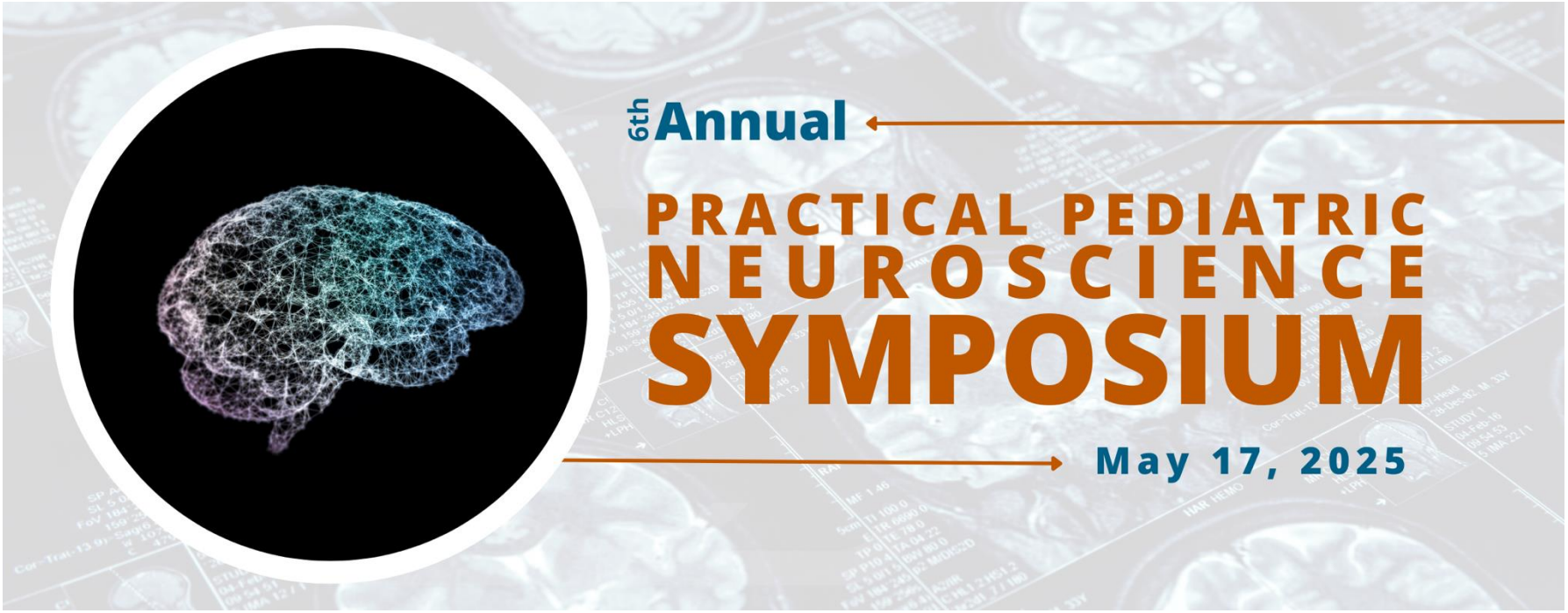

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