Challenges in Neuromodulation Therapy

Milton M. Morris, PhD, MBA
Principal
MEH BioMedical, LLC

February 25, 2015

Neuromodulation offers multiple indication therapy

FDA APPROVED

Deep Brain Stim:

Parkinson's Disease, Dystonia, Essential Tremor, Obsessive Compulsive Disorder

Vagus Nerve Stimulation:

Depression, Epilepsy

Spinal Cord:

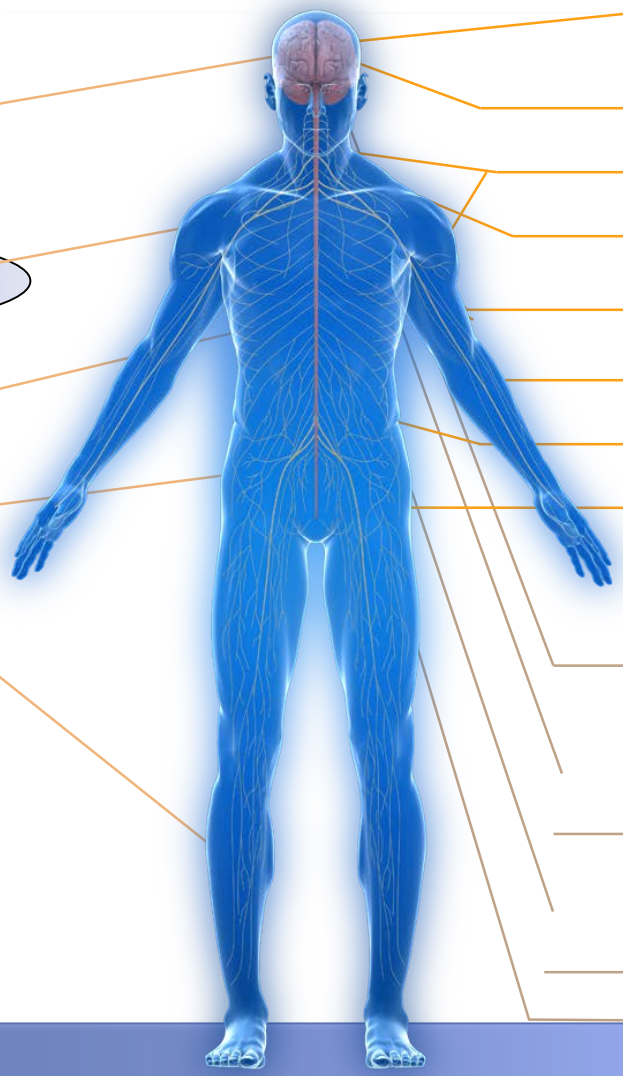
Pain

Sacral Nerve Stim:

Urinary Incontinence, Fecal Incontinence

Percutaneous Tibial Nerve Stim:

Urinary Incontinence



EMERGING

Deep Brain Stim: Obesity, Stroke Recovery, Depression

Cortical Stim: Epilepsy

Peripheral Nerve Stim: Migraines, Extremity Pain

Carotid Artery, Sinus Stim: Hypertension

Hypoglossal & Phrenic Nerve Stim: Sleep Apnea

Spinal Cord Stim: Angina

Gastric Stim: Obesity

Sacral & Pudendal Nerve Stim:
Interstitial Cystitis, Sexual Function, Pelvic Pain

FUTURE

Deep Brain Stim:

Alzheimer's, Anxiety, Bulimia, Tinnitus, Traumatic Brain Injury, Tourette's, Sleep Disorders, Autism, Bipolar

Vagus Nerve Stim:

Alzheimer's, Anxiety, Obesity, Bulimia, Tinnitus, Obsessive Compulsive Disorder, Heart Failure

Spinal Cord Stim: Asthma

Gastric Stim: Bulimia, Interstitial Cystitis

Epilepsy by the numbers

Status of Neuromodulation Therapy(ies)

- FDA: Approved
- CMS: Favorable Coverage Recommendation

Epilepsy

4th most common neurological disease after migraine, stroke and Alzheimer's disease

9 MILLION

People living with epilepsy in United States, Europe, and Japan

<3% chance of seizure freedom after 2 AED failures

400,000

People indicated for VNS Therapy® in US

Direct and indirect costs of **$13.5B** per year in US alone

25-40X

Mortality rate vs. general population

Source: CDC, WHO, IOC report on Epilepsy

Depression by the numbers

Status of Neuromodulation Therapy(ies)

- FDA: Approved (VNS)
- CMS: Non-Favorable Coverage Recommendation

Depression

Major depressive disorder (MDD) is the second leading cause of disability worldwide*

18 MILLION

People affected at any one time in United States

350 Million

People worldwide affected by depressive illness

4 Million

approx. 25% of depressed individuals (U.S.) are treatment resistant

Direct and indirect costs of

> $43B

related to lost productivity in the workplace per year

>39,000

Suicide deaths per year in the U.S.

Source: CDC, WHO, NAMI

*(Ferrari et al, 2013)

Heart Failure by the numbers

Status of Neuromodulation Therapy(ies)

- FDA: Human Clinical Trials (Pivotal & Pilots)
- CMS: NA

Heart Failure

is a serious and progressive condition; incidence increases dramatically with age

10-12 Million

people living with heart failure in the US and Europe

5-Year Mortality

for 50% of patients

700,000

newly diagnosed cases annually

Direct and indirect costs of

$40B

per year in US alone

Most Common Reason

for hospitalization in Medicare patients

Industry Challenges in the Neuromodulation Field

Limitations in Funding Driven by Inconsistent Performance/Results:

- Recent history of study failures has limited investment and innovation
  - CVRx, NorthStar, Apnex, Transneuronix, Cyberonics (depression), Boston Scientific (heart failure), many others
  - What are key learning's to improve success, or to fail fast?
- Lengthy clinical studies and long regulatory processes
  - Can dampen enthusiasm for investment and innovation
- Reimbursement challenges
  - FDA approval does not guarantee national reimbursement coverage

Industry Challenges in the Neuromodulation Field

Limitations of Clinical Past/Current Clinical Studies:

- Implantable neuromodulation therapies are typically indicated for drug refractory, treatment-resistant patients
  - Difficult to treat patient population (different etiologies, phenotypes, patient's physiology and co-morbidities, etc.)
- Difficult to do a blinded study, control group can perceive low levels of stimulation
- The clinical effect is not always obvious and treatment effect may take extended time (months)
- For many therapeutic approaches, no quantitative endpoints are known/available, only qualitative end points
- Animal models may not translate well to human

Industry Challenges in the Neuromodulation Field

Limitations in Known Technology, Science, & Physiology:

- Technical limitations such as imprecise targeting
  - Which cortical pathways & are they stimulation dependent?
  - How to best modulate neuronal activity (inhibit/excite)?
  - Methods to identify optimal stimulation parameters.

- Clinical therapeutic response may not be immediate or obvious
  - e.g., Depression (1 to 6 months), Parkinson's (immediate)

- Limited sensing capability
  - Biomarkers of response are not readily identifiable in today's approved treatments.

- Response Prediction: Identify patients that will respond to therapy prior to implantation.

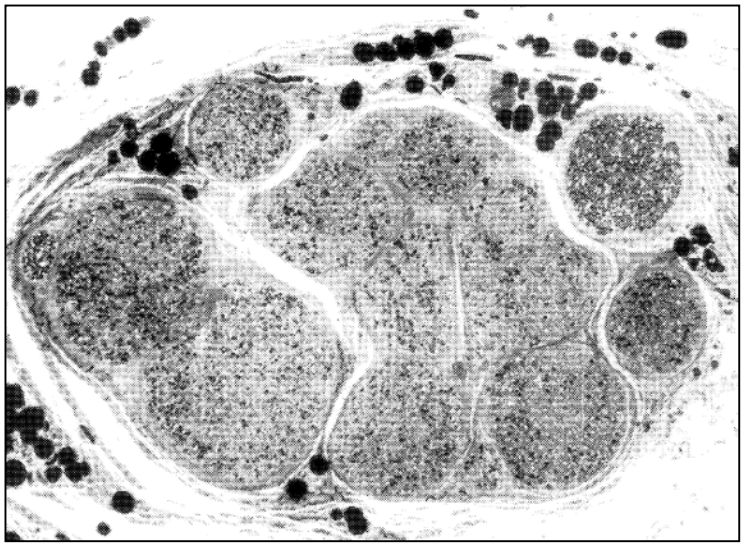
- Incomplete knowledge of mechanisms of therapeutic action

Human Cervical Vagus Nerve

The human vagus nerve

- ~ 100,000 axons
- 80% afferent, 20 % efferent
- 80% are C-fibers, 20% are A, B fibers

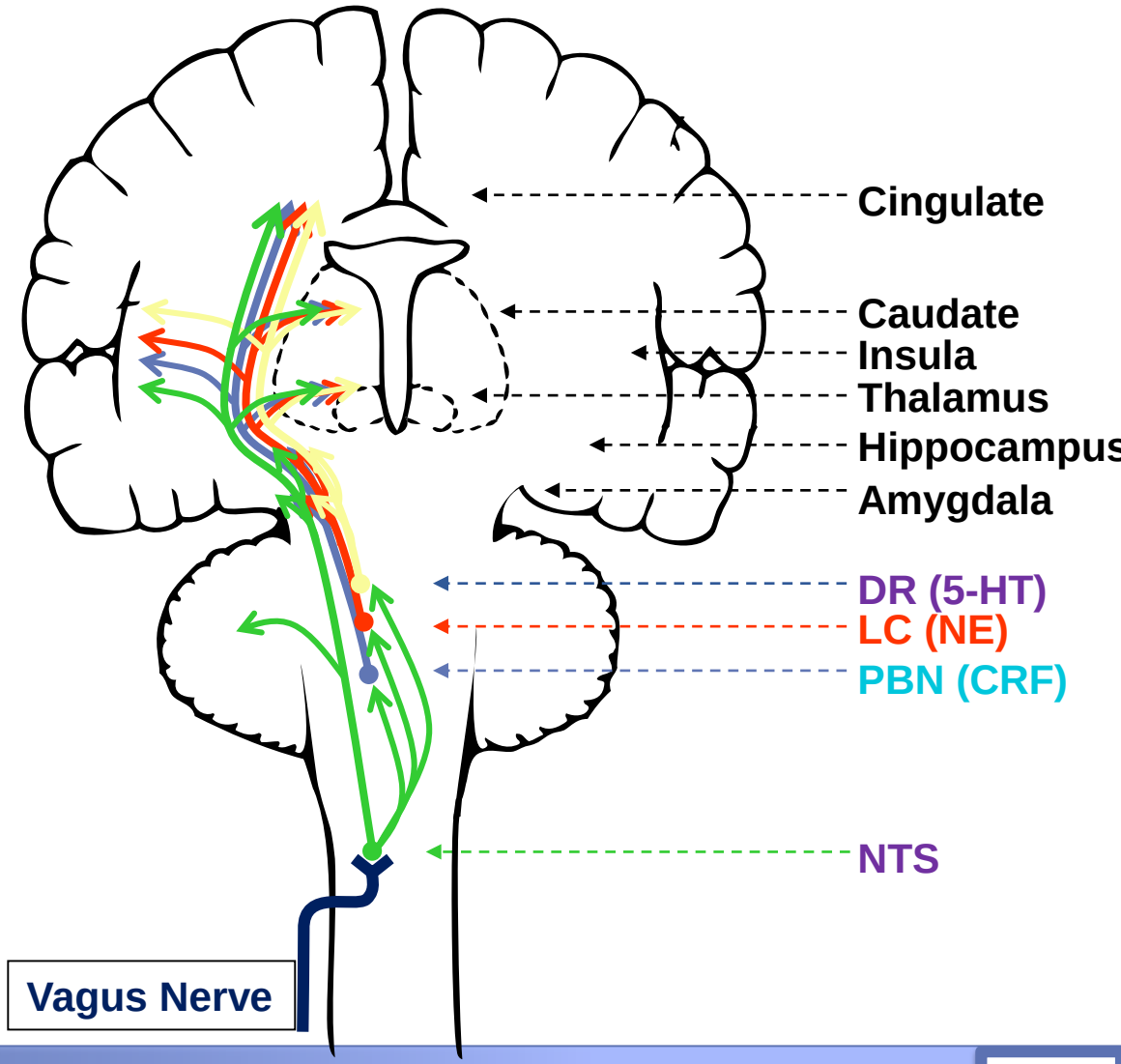
- Which fibers are responsible for therapeutic effect?
- Where do these fibers project into the CNS and peripherally?
- What neuromodulatory systems are excited/inhibited?



Nemeroff CB. *Neuropsychopharmacology.* 2006;31):1345-55.

The Cranial Nerve Highway & Vagus Nerve Stimulation

- ***Bilateral*** projections on nucleus tractus solitarius (NTS)
- Locus coeruleus supplies norepinephrine
- Raphe magnus nuclei supply serotonin
- Parabrachial nucleus of pons has widespread cerebral projections

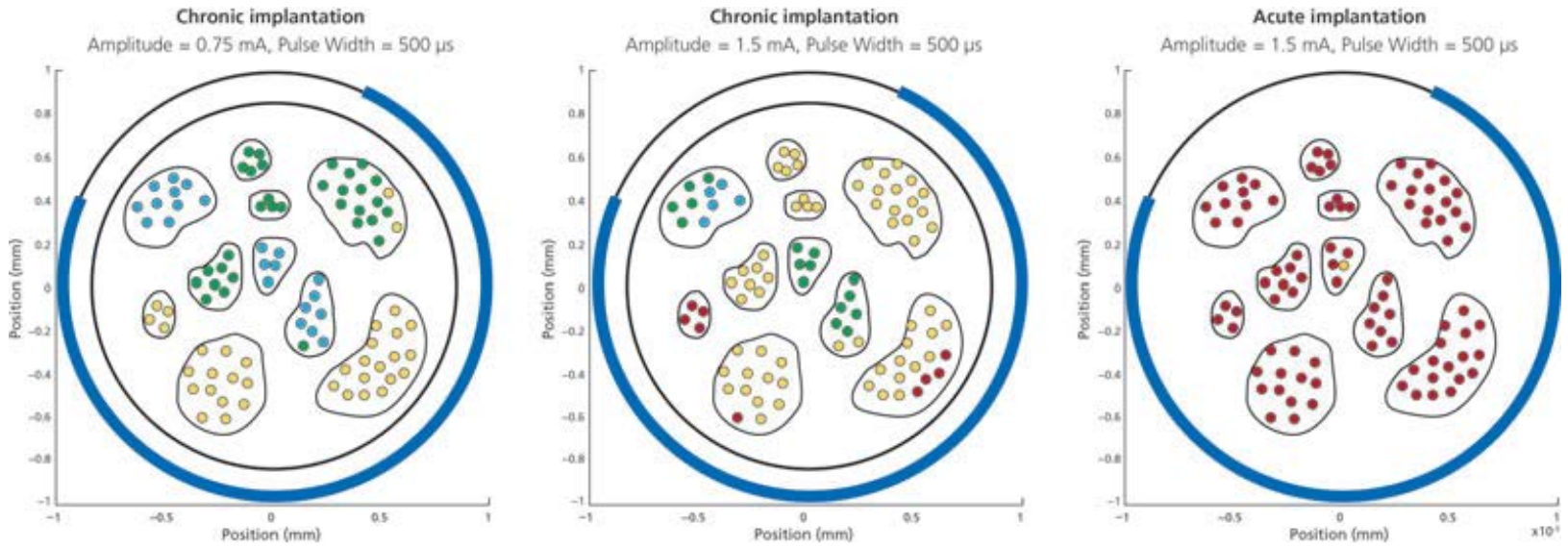


Henry TR. *Neurology.* 2002;59(suppl 4):S3-S14.

Nerve Fiber Stimulus Activation

Vagus nerve cross section, dispersed fiber (axon) types

- Electric fields modeled using finite element (ANSYS)
- Comparison of fiber activation in chronic vs. acute implant
- % fiber activation function of: charge/density, dist. from electrode, acute vs chronic condition
- Challenge: How can we best activate the right fiber groups but minimize adverse events?
  - Incorporate nerve action potential sensing?



Helmers et al. 2012

Summary Challenges (& Opportunities)

for advancing the field of neuromodulation

Challenges: Understanding the "neural code"

- What are the mechanisms of action that lead to positive reproducible outcomes?
- How can stimulation parameters be optimized for specific patients?
- How can we make relevant biomarkers available in real-time?
  - Closed-Loop stimulation
- Can plasticity effects of neuromodulation be predicted?
  - Improved clinical trial Designs

Opportunities: Novel Technologies and Tools

- Advanced brain imaging technologies
- Optogenetics
- Big Data
- Nanotechnologies
- Signal processing methods, Adaptive algorithms

Challenges in Neuromodulation Therapy

Thank You

Milton M. Morris, PhD, MBA
Principal
MEH BioMedical, LLC

February 25, 2015