Neuromodulation

Week 8

Why Neuromodulation?

- Current medical treatments insufficient to combat a variety of neurological and psychiatric disorders
- Made possible through advances in:
  - Understanding of pathophysiology
  - Structural and functional brain imaging
  - Neurosurgical techniques (neuronavigation and microelectrode recording)
  - Neurosurgical equipment (stimulating electrodes, pulse generators, drug delivery pumps)

Why Neuromodulation?

Reversible

Programmable

Specific

TABLE 3.1 Summary of deep cerebral targets and indications for neuro-modulation

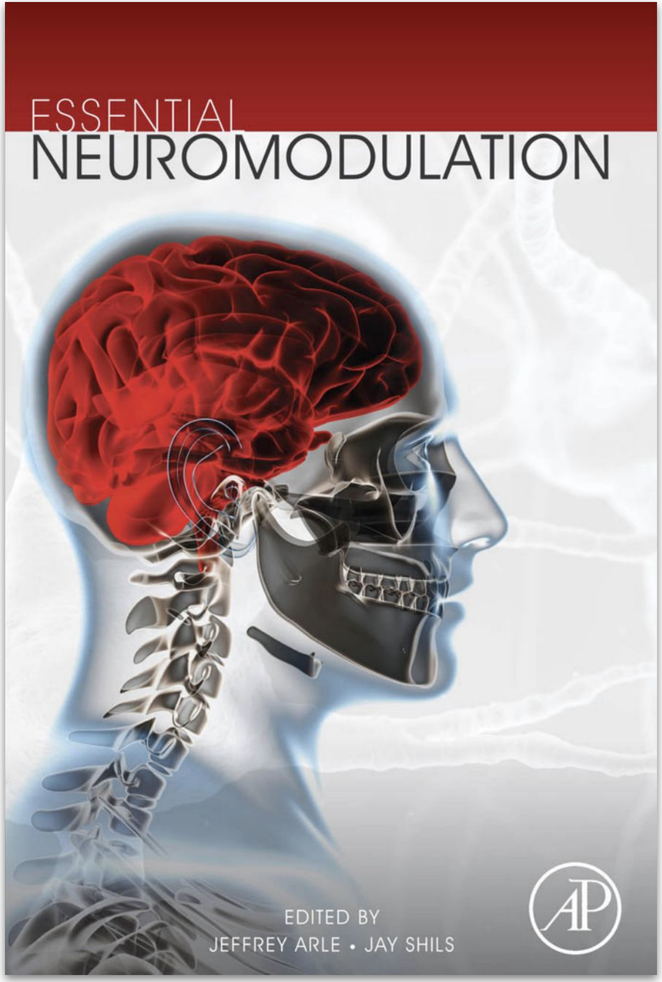
Disease/disorder	Target
Pain	
Nociceptive	Periventricular/periaqueductal gray (PVG/PAG)
Neuropathic	Ventrocaudal thalamus
Tremor	
Essential tremor*	Ventrolateral thalamus#
Parkinsonian tremor*	Zona incerta/pre-lemniscal radiation
Intention tremor	
Parkinson's disease*	
Rigidity	
Bradykinesia	Posteroventral globus pallidus pars internus #
Levodopa-induced dyskinesia	Subthalamic nucleus#
Motor fluctuations	
Tremor	
Gait akinesia and postural instability	Pedunculoponinte nucleus (PPN)
Dystonia	
Primary generalized dystonia*	Posteroventral globus pallidus pars iInternus#
Secondary dystonia	Subthalamic nucleus#
	Ventolateral tThalamus
Epilepsy	
Remote from the epileptogenic focus	Cerebellum Centromedian nucleus of the thalamus Anterior nucleus of the thalamus Subthalamic nucleus Head of the caudate nucleus
At the epileptogenic focus	Cortical Mesial temporal lobe (MTL)
Tourette's syndrome	Centromedian nucleus of the thalamus Posteroventral globus pallidus pars interna Anteromedial globus pallidus pars interna Nucleus accumbens (NAc) and anterior limb of internal capsule (IC)
Obsessive–compulsive disorder*	Ventral capsule/ventral striatum (VC/VS)# Nucleus accumbens
Depression	Subgenual cingulate cortex (Brodmann's area 25) Rostral cingulate cortex (Brodmann's area 24a) Ventral striatum/nucleus accumbens Inferior thalamic peduncle Lateral Habenula
Addiction	Nucleus accumbens
Obesity	Ventromedial hypothalamus

The current list of proposed indications and potential deep cerebral targets for neuromodulation are presented.
Indicates an approved indication.
#*Indicates an approved target for the given indication. (NB: Dystonia and obsessive–compulsive disorder are approved in the USA under a 'Humanitarian Device Exemption')*

Essential Neuromodulation

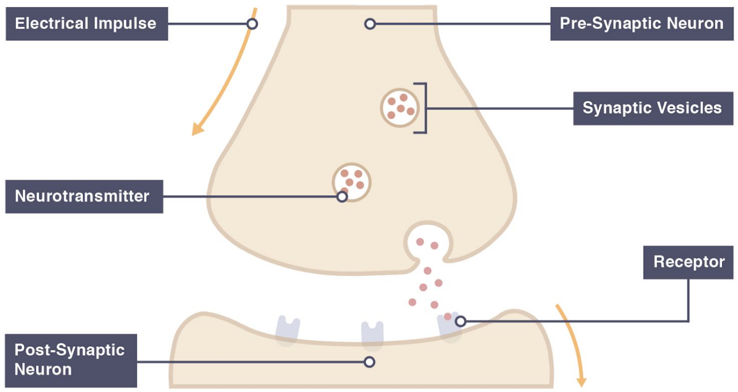
Jeffrey Arle & Jay Shils

Free PDF copy available online



What is Neuromodulation?

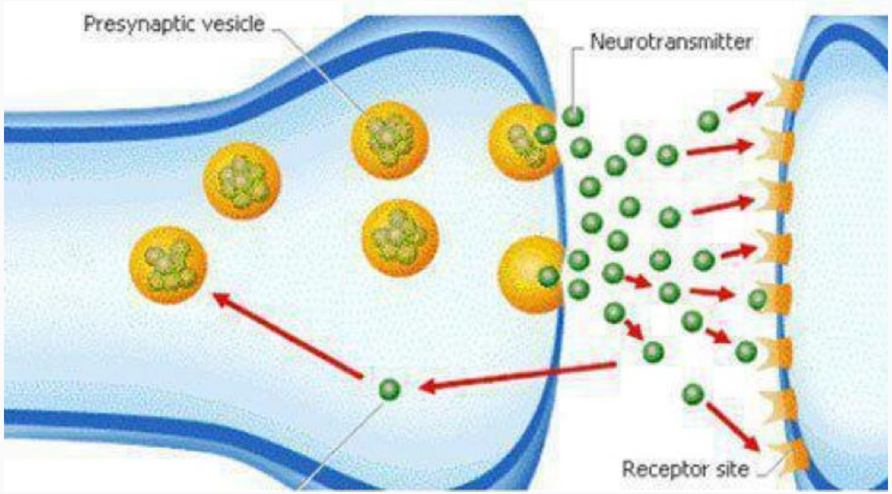
- Targeted release of a substance from a neuron that can do one of the following:
  - Alter efficacy of synaptic transmission
  - Alter synaptic properties of pre-synaptic neuron
  - Alter synaptic properties of post-synaptic neuron



- The physiological process by which a neuron uses one or more of its neurotransmitters to regulate diverse populations of neurons

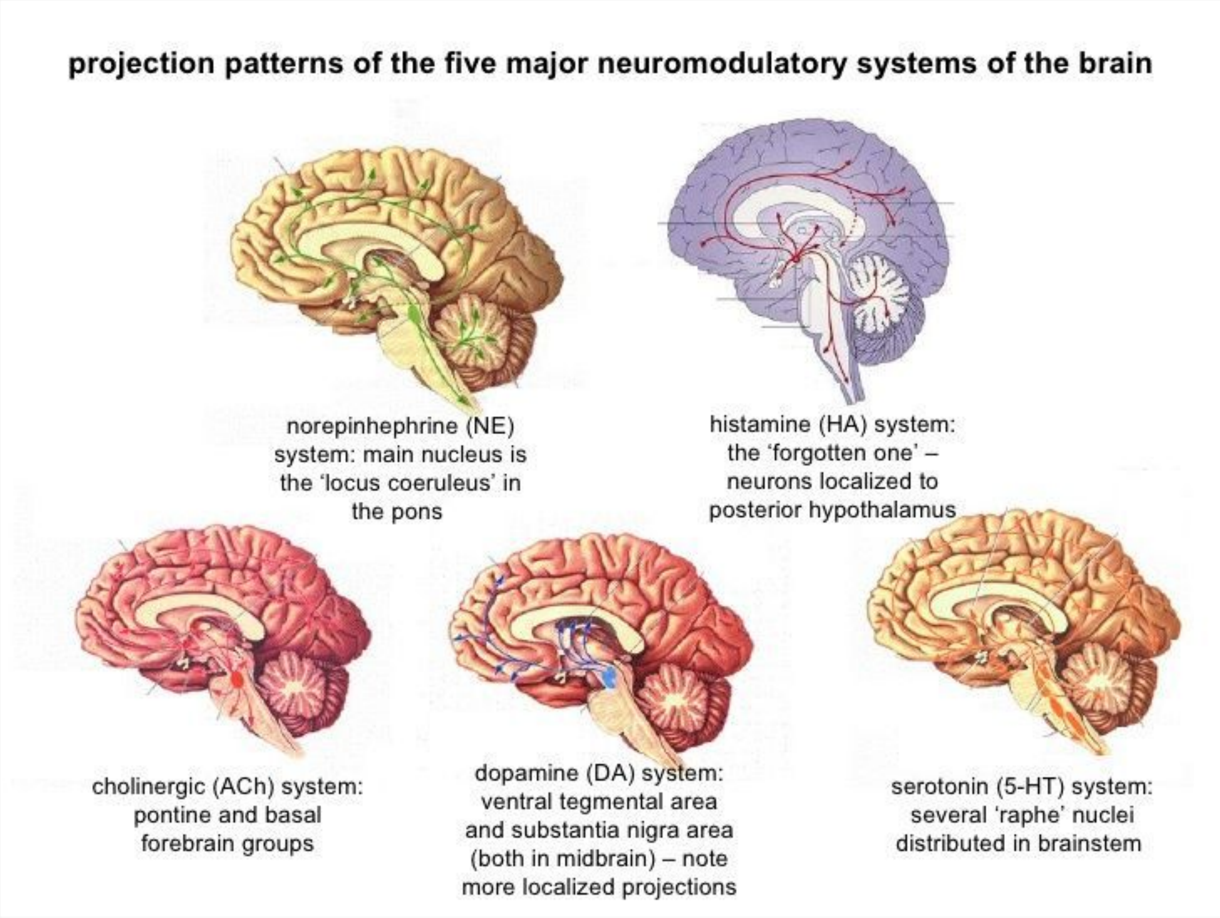
Neurotransmitters

- A substance that gets released by a neuron at a synapse to affect another cell (e.g., another neuron)



Neuromodulators

- Neuromodulators are neurotransmitters that have spatially distributed effects on recipient neurons and neural circuits
- Neuromodulators secreted by a **small group of neurons** can diffuse through large areas of the nervous system and affect **multiple neurons**
- Major neuromodulators in the CNS:
  - Norepinephrine
  - Histamine
  - Acetylcholine
  - Dopamine
  - Serotonin

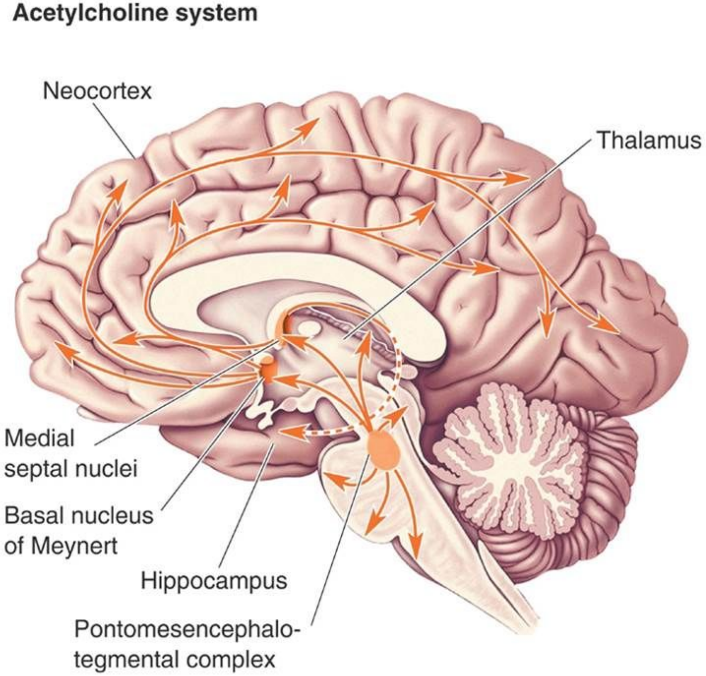


Neuromodulatory Systems

- Ascending Systems (projections from brainstem and basal forebrain to broad areas of CNS)
  - **Cholinergic**
  - **Dopaminergic**
  - **Serotonergic**
  - **Adrenergic**

Acetylcholine (Cholinergic System)

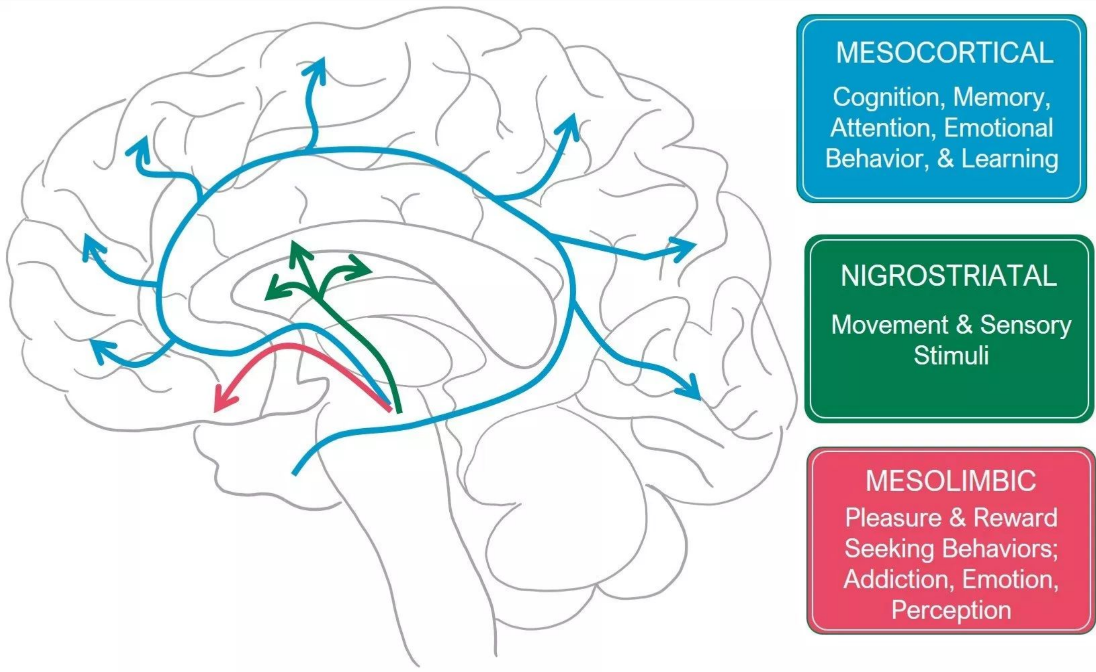
- Can influence thermoregulation, sleep patterns, food intake, endocrine functions (i.e. insulin/glucagon release)
- ACh signalling might be important in stress response → stress increases its release in the brain



Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

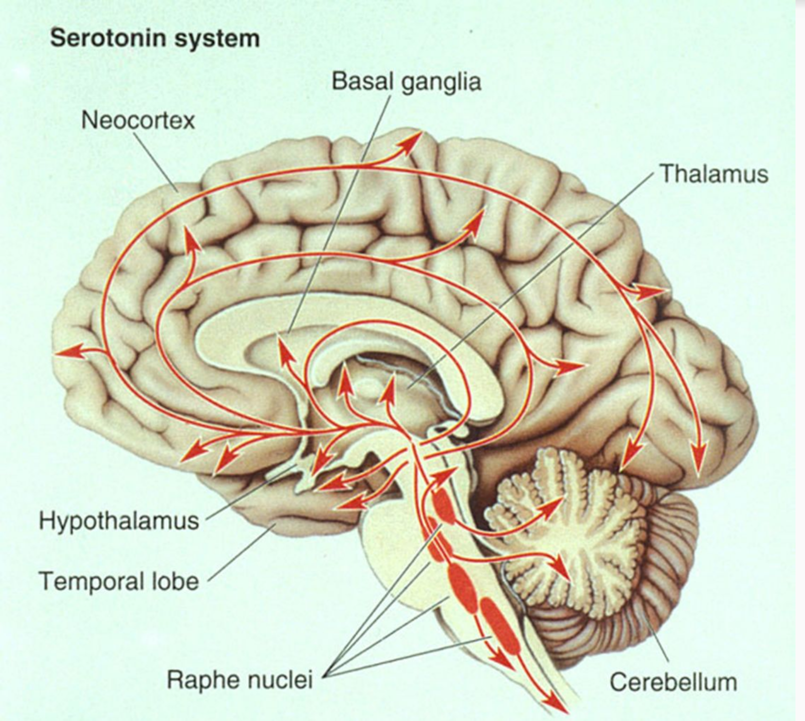
Dopamine (Dopaminergic System)

- Centrally involved in reward, exploration, approach behaviour, and various aspects of cognition
- Variations in this neuromodulator appear to be associated with variations in personality



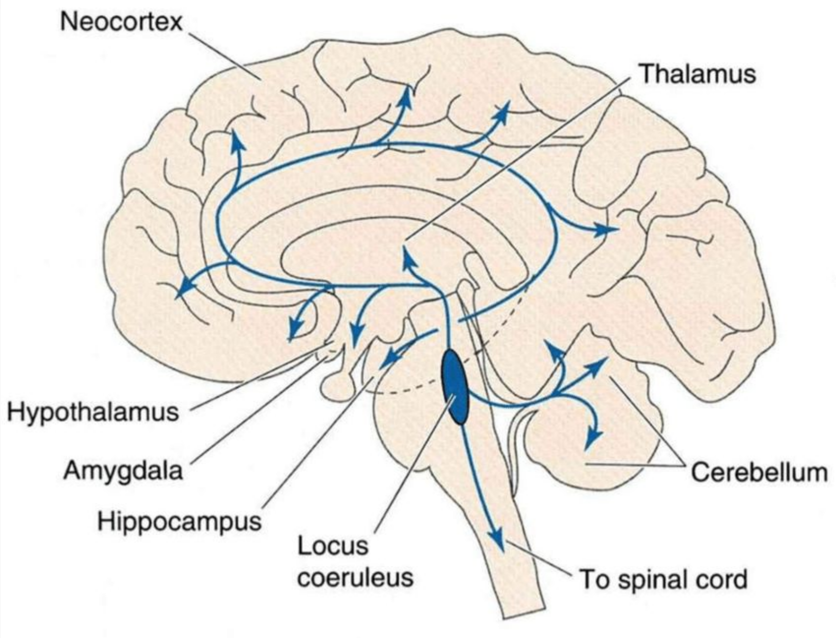
Serotonin (Serotonergic System)

- Serotonin plays a major role in regulating mood and anxiety
- 90% of the body's serotonin is found in the gastrointestinal tract where it has a role in regulating bowel function and movements
- Also is responsible for satiety (reducing appetite while consuming a meal)



Noradrenaline (Adrenergic System)

- Regulates activity of neuronal and non-neuronal cells
- Participates in modulation of cortical circuits and cellular energy metabolism (rapid) and inflammation and neuroplasticity (slow)
- Found in many regions of the brain, but the **locus coeruleus** plays a major role in noradrenergic signalling
- Plays a critical role in modulating plasticity, learning, and memory via the **hippocampus** in the brain



How does it work?

- Neuromodulation works by either actively **stimulating nerves** to produce a natural biological response or by applying targeted **pharmaceutical agents** in tiny doses directly to the site of action

- Neurostimulation devices involve the application of **electrodes** to the brain, the spinal cord or peripheral nerves

Applications of Neuromodulation Technology

Modulation of nerve activity by delivering electrical or pharmaceutical agents directly to a target area

- Deep brain stimulation (DBS) treatment for Parkinson's disease
- Sacral nerve stimulation for pelvic disorders and incontinence
- Spinal cord stimulation for ischemic disorders
- Cochlear implant to restore hearing for deafness

Tech Feature

- **BrainGate Neural Interface System** - can analyze brain signals and translate them into cursor movements
- Grants severely motor-impaired individuals an alternate “pathway” to control a computer with their thoughts
- Offers potential for restoring some degree of limb movement

Cortical Control of a Tablet Computer by People with Paralysis

Nuyujukian*, Albites Sanabria*, Saab*, Pandarinath, Jarosiewicz, Blabe,
Franco, Mernoff, Eskandar, Simeral, Hochberg**, Shenoy**, Henderson**

PLOS ONE, Nov. 21, 2018

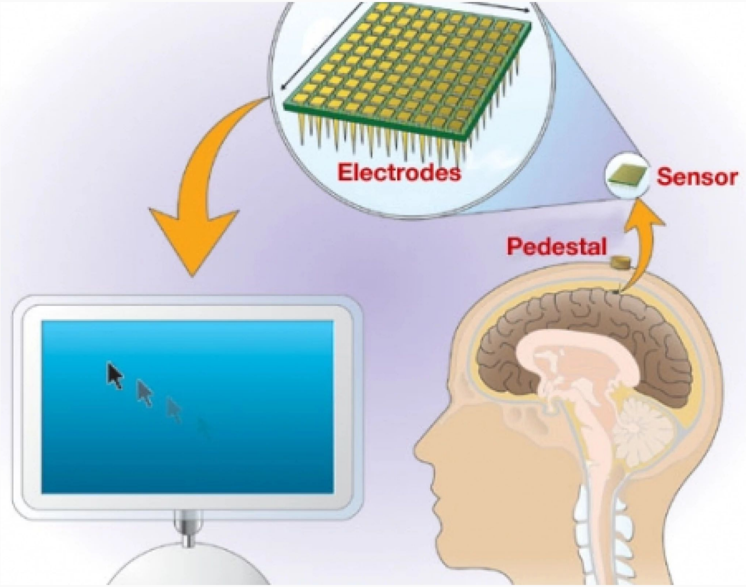
BRAINGATE

BrainGate2 Pilot Clinical Trial
Caution: Investigational Device. Limited
by Federal Law to Investigational Use.

MGH
1811

How is this Possible?

- Device Components:
  - Internal neural signal sensor
    - Consists of a tiny chip with 100 electrode sensors that can detect brain cell electrical activity
    - Implanted into the **motor cortex area** (controls movement)
  - External processors
    - These computers convert neural signals (controlled by the user) into output signals (communication) using custom decoding software



Future Directions

Paralysis Treatment

- Implant **stimulators that connect to both brain signals and muscles**, using electrical impulses created by the system's hardware to **allow people with paralysis to move their arms**

Epilepsy Monitoring

- Implant **brain sensors to measure minute changes in brain activity** which may be used to **detect warning signs** like the onset of an epileptic seizure

BrainGate vs. Neuralink

Compared to BrainGate, Neuralink's device has:

- Many more electrodes for data transfer (100 vs. 1000)
- Material composition better matched to properties of human brain tissues

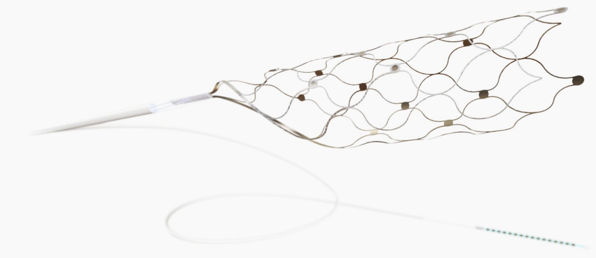
BrainGate birthed BCIs as a research field, but it looks like Neuralink will be filling its shoes

Stentrode: A Breakthrough Device

- FDA designated Stentrode as a “breakthrough device” in 2020
- What is Stentrode?
    - A fully-implantable device that **can translate brain activity or stimulate the nervous system from the inside of a blood vessel**—no need for open brain surgery
- **Safer** than BrainGate and Elon Musk’s Neuralink, which both require drilling into the skull for device insertion

From Neuromodulation to Neuroprosthesis

How Synchron's tech works with paralysis



- **Stentrode** is inserted into a blood vessel to capture brain signals related to intended movement and stimulate the nervous system
- **BrainPort** is implanted in the chest (similar to a pacemaker) and receives brain data from the Stentrode to wirelessly transmit to BrainOS

From Neuromodulation to Neuroprosthesis

How Synchron's tech works with paralysis

- **Stentrode**
- **BrainPort**
- **BrainOS** is an app platform that transforms the brain data into a standardized digital language, controlling apps and potentially other digital devices, or telling BrainPort to stimulate the nervous system through Stentrode

Future of Deep Brain Stimulation (DBS)

- FDA has approved the investigation of DBS use in:
  - Depression
  - Alzheimer’s disorder
  - Addiction
  - Headache
- **DBS traditionally requires open brain surgery**—Synchron’s Stentrode overcomes this safety risk

Limitations of Stentrode

Device must become substantially smaller in order to fit in smaller blood vessels modulating regions like the thalamus, fornix, nucleus accumbens, subgenual cingulate white matter, and ventral capsule

Possible safety issues: vascular injury, infection, stenosis, and thrombosis

Limitations of Stentrode

Wires connecting Stentrode to BrainPort are limiting:

- May impede medical monitoring at implantation site
- May prevent IV injections
- May cause blood vessel rupture, internal bleeding

Potential solution: scale down electronics of BrainPort to be included within Stentrode, eliminating need for wires

More on Stentrode:

Taylor & Francis
Taylor & Francis Group

Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

The future potential of the Stentrode

Sam E. John, David B. Grayden & Takufumi Yanagisawa

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To link to this article: https://doi.org/10.1080/17434440.2019.1674139

BrainGate vs. Neuralink vs. Synchron

Who is leading?

- In terms of human trials and regulatory approvals: **Synchron**
- In terms of signal accuracy: **Neuralink**