Neurosurgery and Medicine: Testing Ground for Network Physiological Methods?

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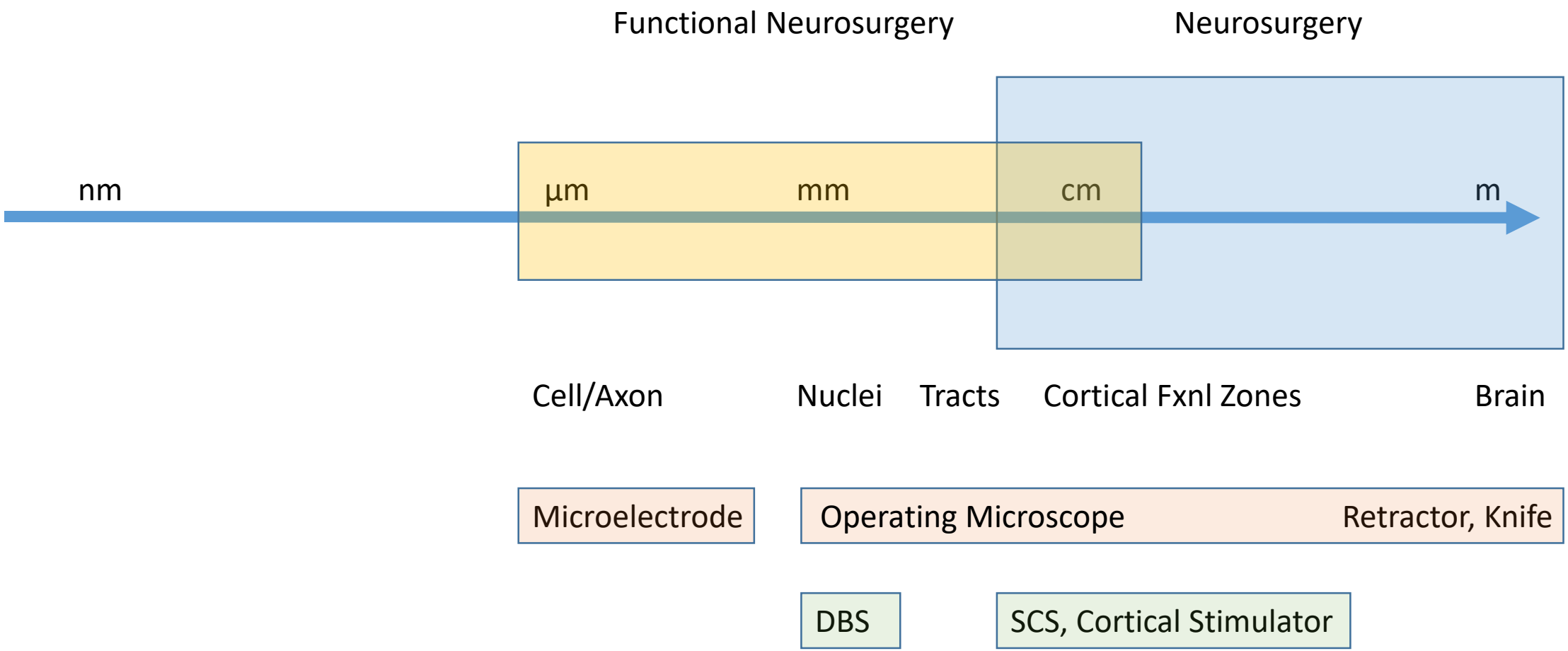
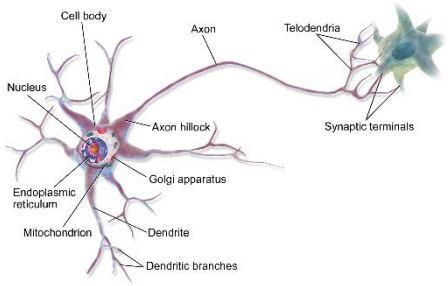
Problems in Neurosurgery

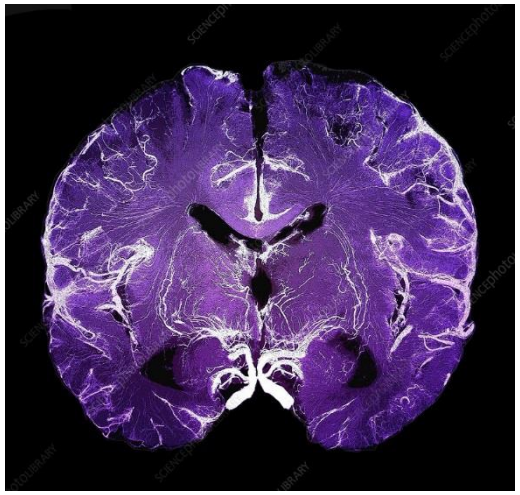
- Determining (pre op, intra op) **effects** of resection and brain manipulation
- **Real time** and expected long term effects of stimulation (blockade, synchronization)
- Accurate (physiologic) **targeting** of CNS structures
- **Classification and management** of unconscious (COMA) states
- **Classification and management** of traumatic brain injures (severe to mild – concussion)
- **Optimized management** of patients with severe CNS pathology and altered physiology (trauma, SAH)
- **Optimized integration-manipulation** of systemic elements (cardiopulmonary, renal, metabolic, endocrine) in setting of CNS pathology

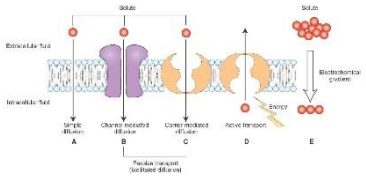
Limitations

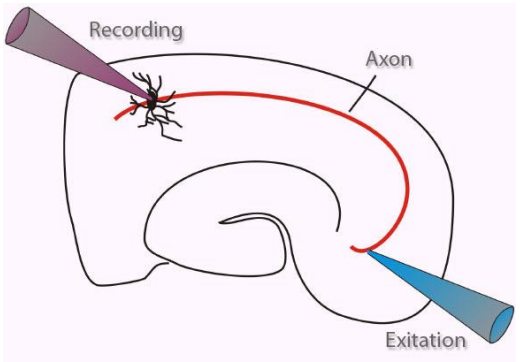
- Absent “ground truth” regarding brain anatomy and function
- Manipulation (surgical) is poorly tolerated
- Biological material (soft, easily injured) that must be moved to operate
- Scales: m (tracts), cm (cortex, nuclei), mm (functional), micro m (cellular), nano m (membranes, channels, synapses, molecular)
- Data: limited largely to “outside the box” measurements
- Data: limited to averages, intermittent sampling, low resolution time series, aggregate

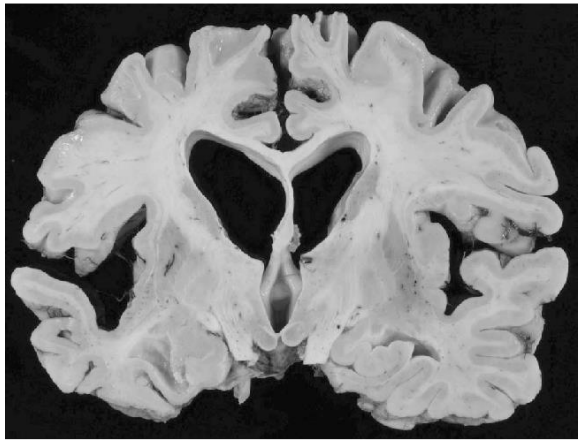

Functional Neurosurgery
Neurosurgery
nm
µm
mm
cm
m
Cell/Axon
Nuclei
Tracts
Cortical Fxnl Zones
Brain
Microelectrode
Operating Microscope
Retractor, Knife
DBS
SCS, Cortical Stimulator

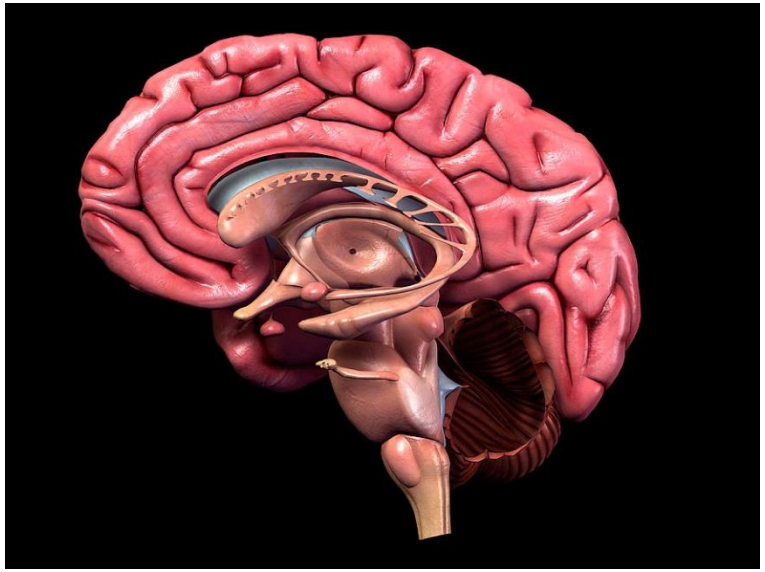

Cell body
Axon
Telodendria
Nucleus
Axon hillock
Synaptic terminals
Golgi apparatus
Endoplasmic reticulum
Mitochondrion
Dendrite
Dendritic branches

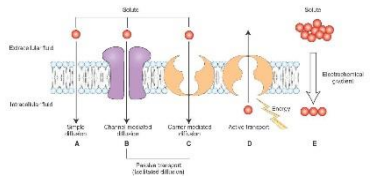


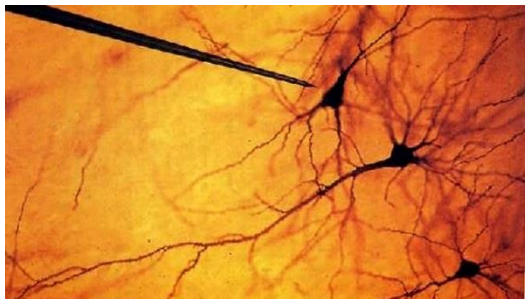


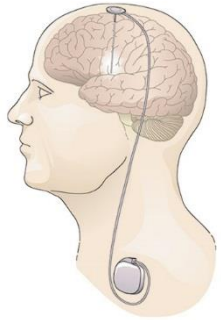

Recording
Axon
Exitation

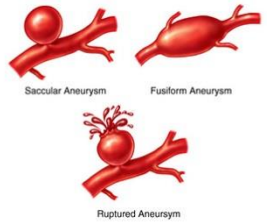


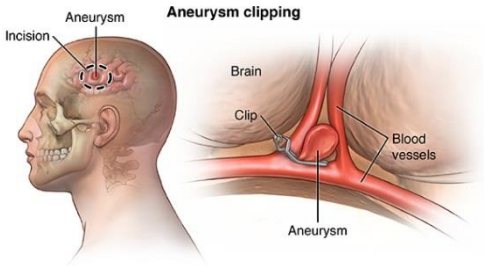


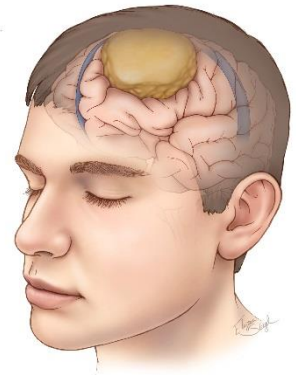












Microelectrode Recording

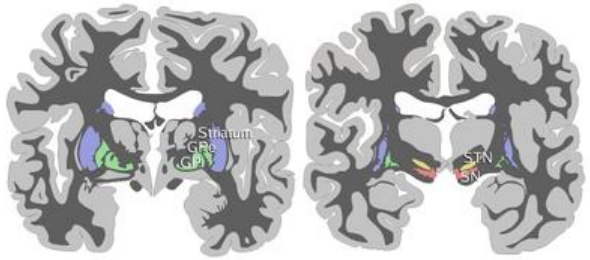
Angiography

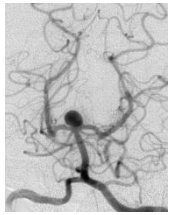
MRI, fMRI, CT, PET

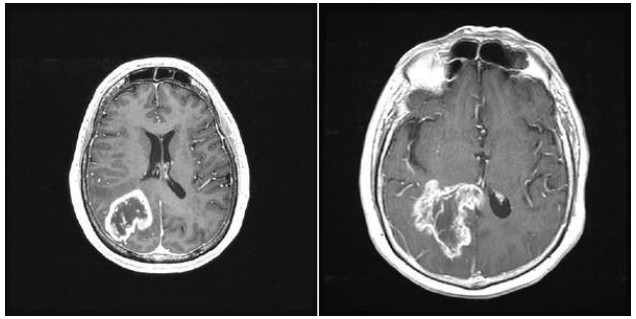
MRI*

Doppler Velocity

EEG







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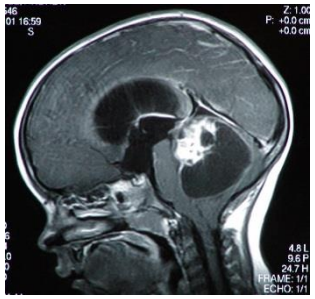

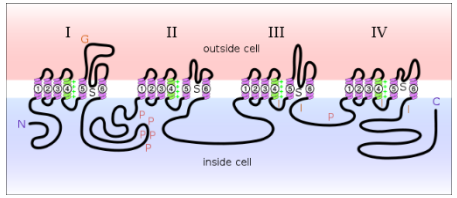

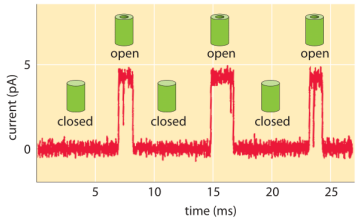

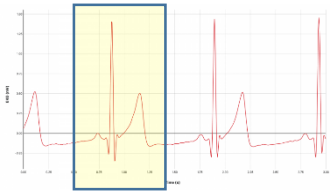

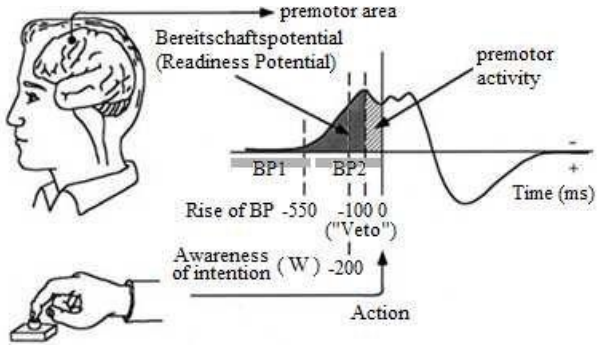

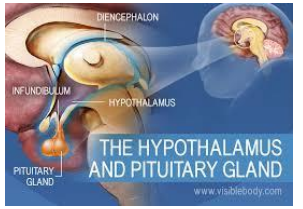

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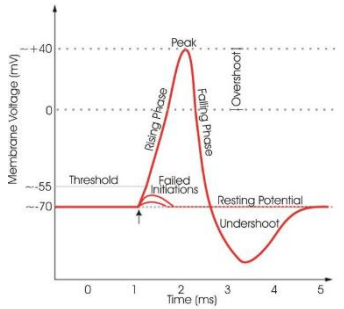
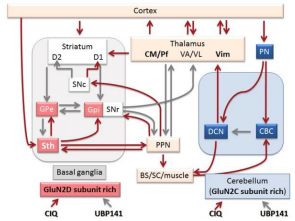
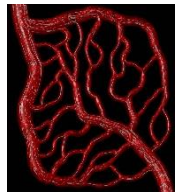
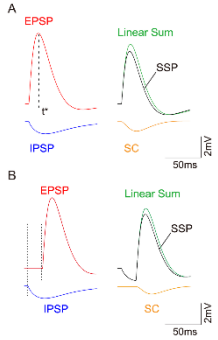
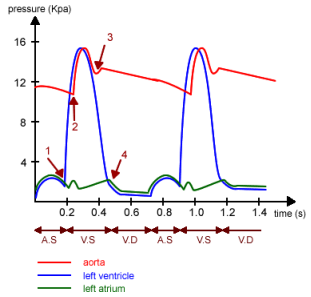






10-15 min
Warm ischemia time





ECG

Cardiac Output

Chemistry (blood, urine)

Arterial Pressure

Temperature

Thermogram

Respiratory Rate, Volumes

End Tidal CO2

O2 Sat (pulse oximeter)

Pulmonary Artery Pressure

Central Venous Pressure

Systemic

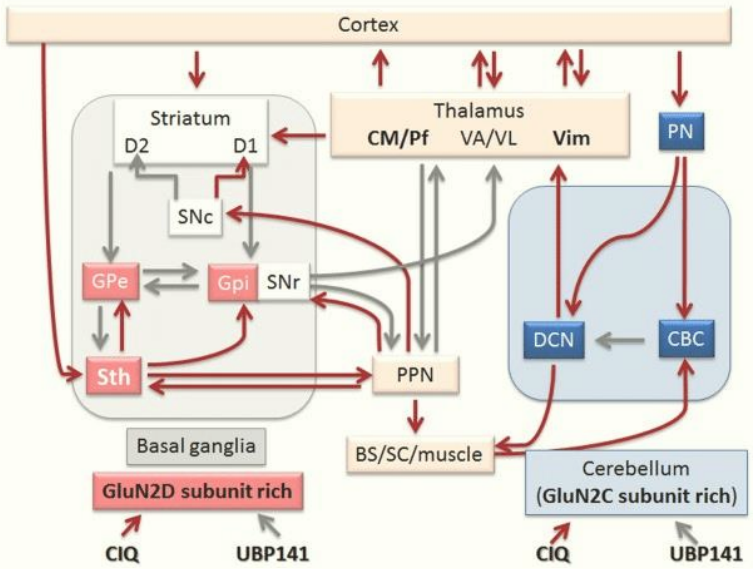
Urine Output

CNS, Brain

EEG (scalp)
EEG (depth electrode)
EEG (surface grid)

Single and multi-unit recording

ICP
CBF velocity
Brain pO2 (local)



CNS

Hypothalamus/ANS → Temperature control, metabolic homeostasis, water/Na control

Hypothalamus-Pit/Endocrine → BMR, thyroid, adrenal, water elimination-retention, reproduction

Medullary, RVL, X → Heart rate, respiratory control, BP control

Skeletal Motor System, Cortical Motor, Cerebellum → Tone, movement, tremor suppression

Brainstem, BG, reticular thalamus → Consciousness
Sleep

SYSTEM

Network and Configuration

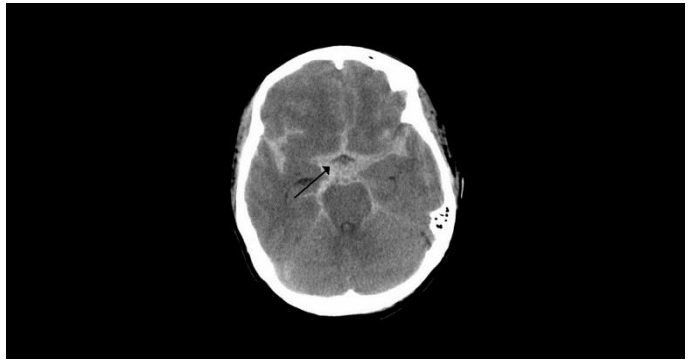
- The language of “state, configuration, network, and coupling of elements” has already found its way deeply into our notions of brain function (isolated), systemic function, and brain-system interaction.
- We lack – however – clinically applicable tools that convincingly identify states defined by coupling of elements that can be used to guide bedside decision-making.
- Q1: *are physiological and pathophysiological (in setting of clinical neurology and neurosurgery) configurations real and meaningful?*
- Q2: *are there any real-life neurosurgical problems that could be approached or investigated using these perspectives, methods, and tools?*

We don’t know --- but I think there are good reasons to explore these possibilities further, especially in the care of patients with neurological disorders.

Clinical Problem-Opportunity 1: COMA

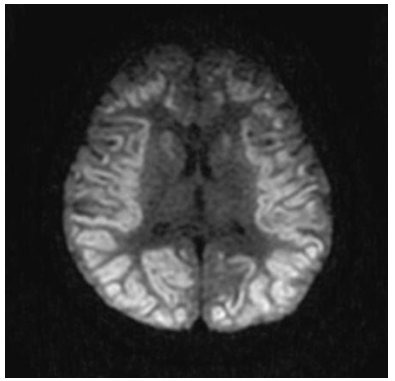
- Many clinical circumstances characterized by loss of consciousness (and normal sleep).
- Causes are variable (trauma, SAH, hypoxic brain injury, toxic encephalopathy)
- On the surface, patients look very similar although the underlying pathophysiology is different and outcomes vary drastically.
- Tools to differentiate cases are crude and descriptive (GCS)
- Prognostication is at best approximate and can be catastrophically inaccurate (good or bad)
- No tools that can reliably define, detect, or identify subgroups.

Cases



Case 1: 50 yo male with diffuse grade IV SAH. Angiography reveals a ruptured anterior circulation aneurysm which is coil occluded to avoid repeat rupture. Patient remains unresponsive for 4 weeks on ventilator support. Vital signs are largely normal throughout hospital course. Eventually, a tracheostomy is placed and patient is transferred to a nursing facility where he never regains consciousness despite imaging that discloses no brain tissue loss. Patient expires 2 years post SAH of complications (infection, pulmonary embolism, malnutrition).

Cases



Case 2: 55 yo female with family history of coronary artery disease is found unconscious and pulseless at home. EMT arrive, intubate and resuscitate the patient. She is admitted to the neurointensive care unit where she remains unresponsive for several weeks. Diagnostic studies reveal the patient has suffered a cardiac arrest from a inferior wall MI. Vital signs are essentially normal and stable throughout the hospitalization. Imaging suggests a diffuse hypoxic brain injury. Hospital day 30 the patient opens her eyes and beings to follow commands. She is extubated and makes a slow but dramatic recovery eventually returning to home and work.

Prognosis and Management

- Some prognostic factors are known in both instances (SAH vs anoxia)
- Hunt and Hess Grade of SAH (how neurologically impaired at outset)
- Fisher Grade of SAH (how much blood)
- Occurrence and severity of vasospasm
- Exposure time to low or zero perfusion
- Age of patient
- Signs of brainstem injury or malfunction
- **OVERALL CARE IS LARGELY SUPPORTIVE**

Hints

- Although systemic factors (BP, etc.) are normalized, the absolute value of vital signs may not be as helpful a guide as **system reactivity** (ANS function and brain-system coupling). Points to brain-system coupling.
- Attempts are made to normalize CBF and ICP but best strategy (target values) may depend on **state of autoregulation** (CPPop). Points to brain-vasculature coupling.
- Metabolic factors probably contribute to outcome (baseline glucose, ph, pCO2). Points to brain-metabolism coupling.
- Neuro suppression (barbiturates, etc.) may be helpful.
- Neuro suppression (hypothermia) may be helpful or harmful.

Issues and Questions

- Can pathophysiologic states (**brain**) of unconsciousness be defined and detected beyond those characterized by etiology and crude grading scales of *apparent* severity?
- Can pathophysiologic states (**brain + system**) of unconsciousness be defined and detected?
- If so, how might this be done? (using clinically available data)
- If so, how might this be useful? (influence on management, path from COMA to wakefulness --- available? Which path?)

Present Model

COMA

Normalize Every Salient Physiologic Factor

Wait



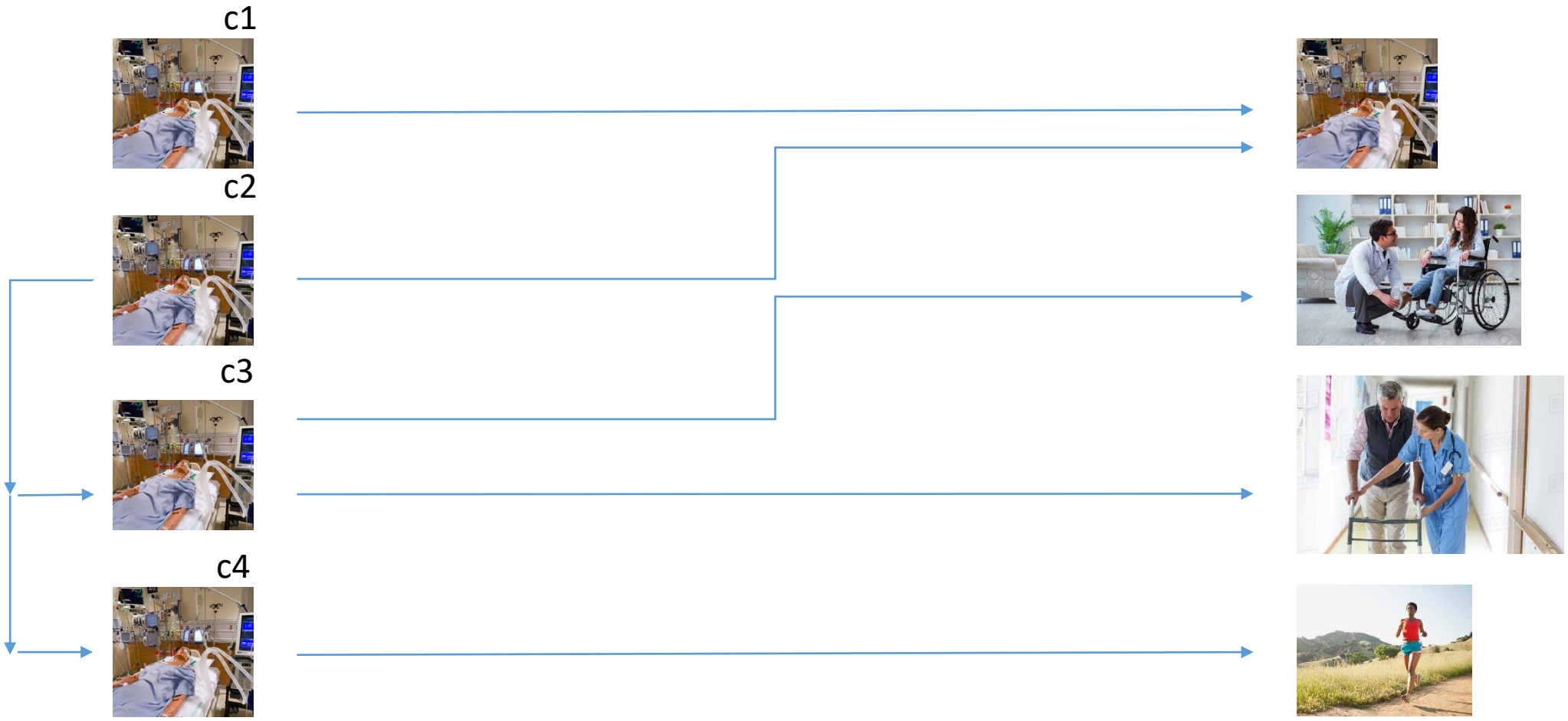




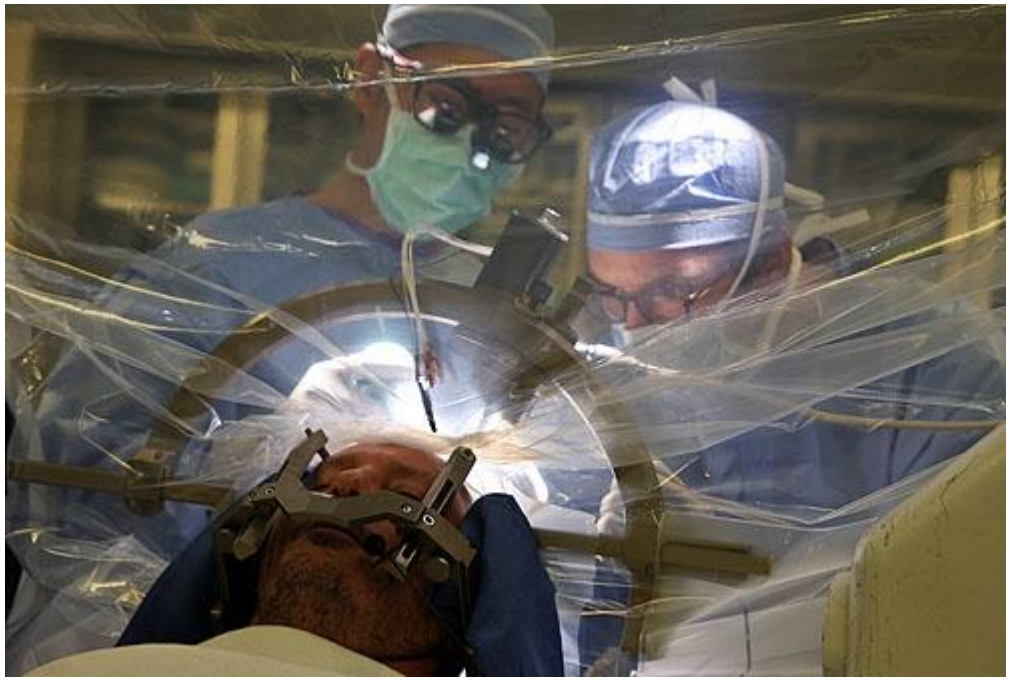


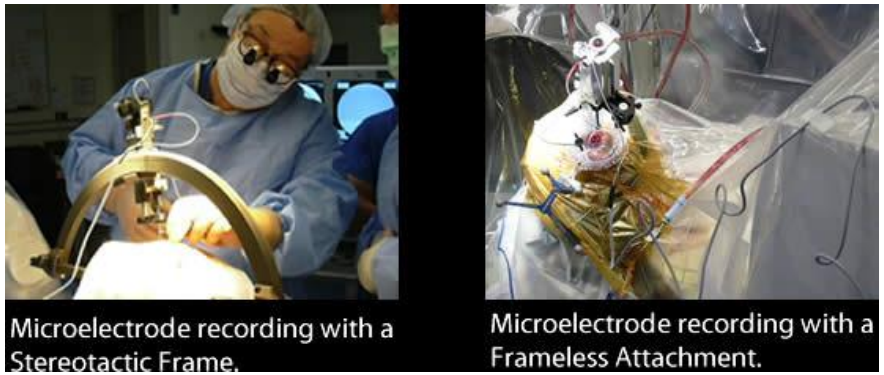


Provisional Concept



Clinical Problem-Opportunity 2: Functional Neurosurgery



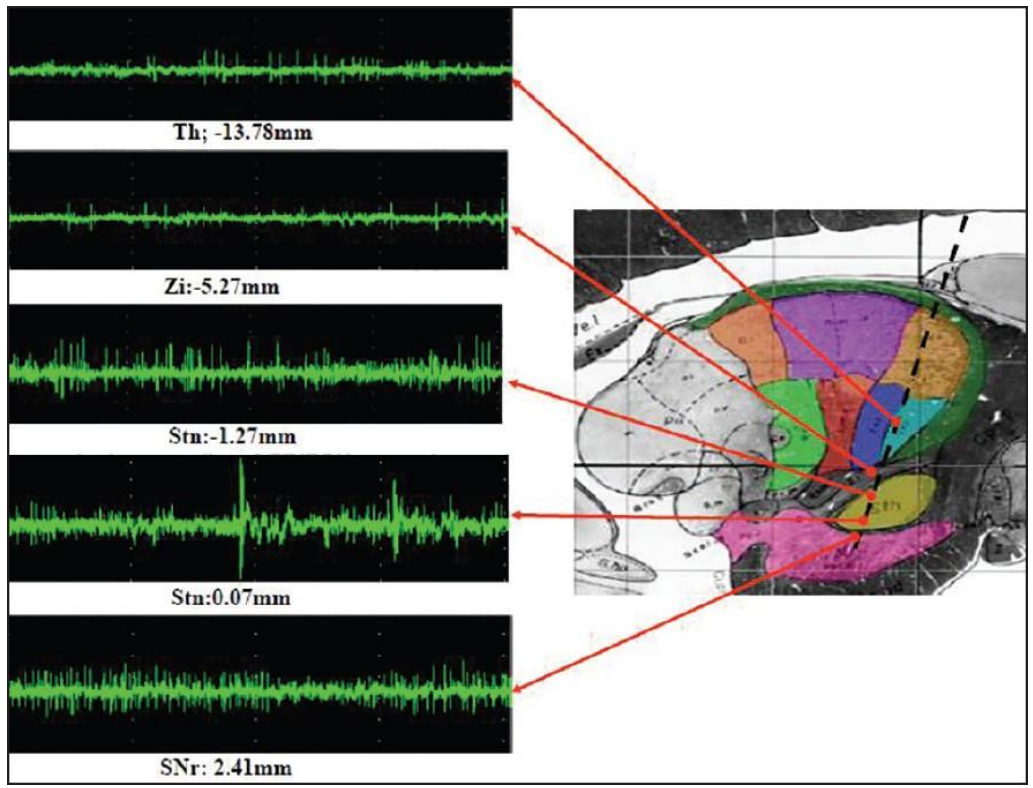


Tool: Functional Neurosurgery

- Ablate saliently overactive regions
- Stimulate target
- Stimulation: a) depolarization block (ablate output), b) synchronize neurons
- Utilize micro electrode recording to identify targets
- Place large permanent stimulating electrodes to achieve block or synchronization
- Notion is to achieve some “normalization” of network function to restore ability to move, eliminate involuntary movements, reduce pain, alter mood, control compulsions, alter hunger

Limits of Functional Neurosurgery

- Incomplete picture of “ground truth” that depicts healthy and pathological network activity
- Incomplete knowledge of possible targets
- Incomplete knowledge of combination effects
- Limited repertoire of effects with stimulation (block regional output, synchronize regional output)
- Limited ability to measure effect (live) of stimulation (no interrogation of network beyond large scale effects on patient in OR)
- Do not collect additional date during stimulation and device placement that may guide target selection (EEG, EMG, multi-target unit activity)
- Individual variation in severity of disease and effects DBS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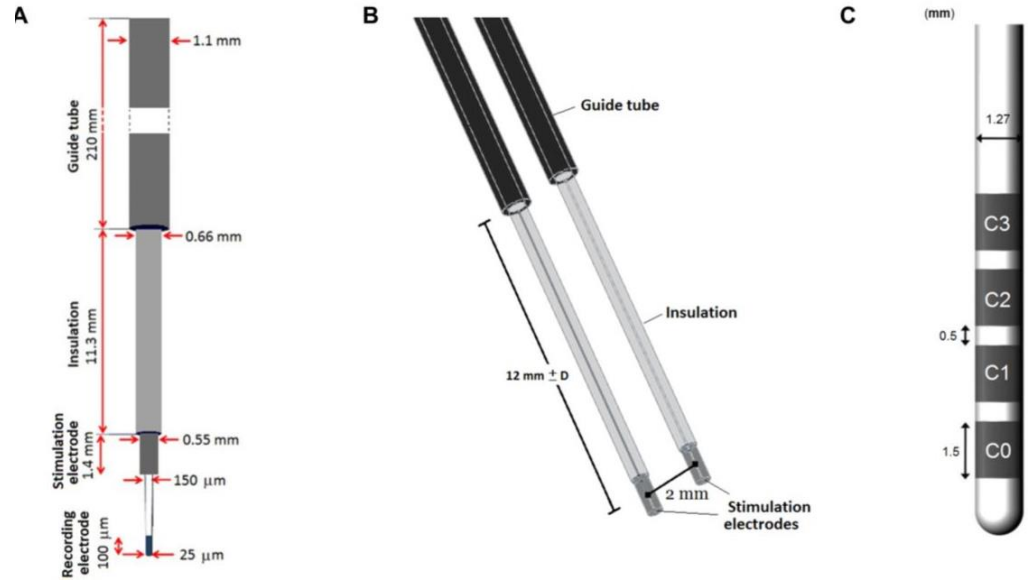
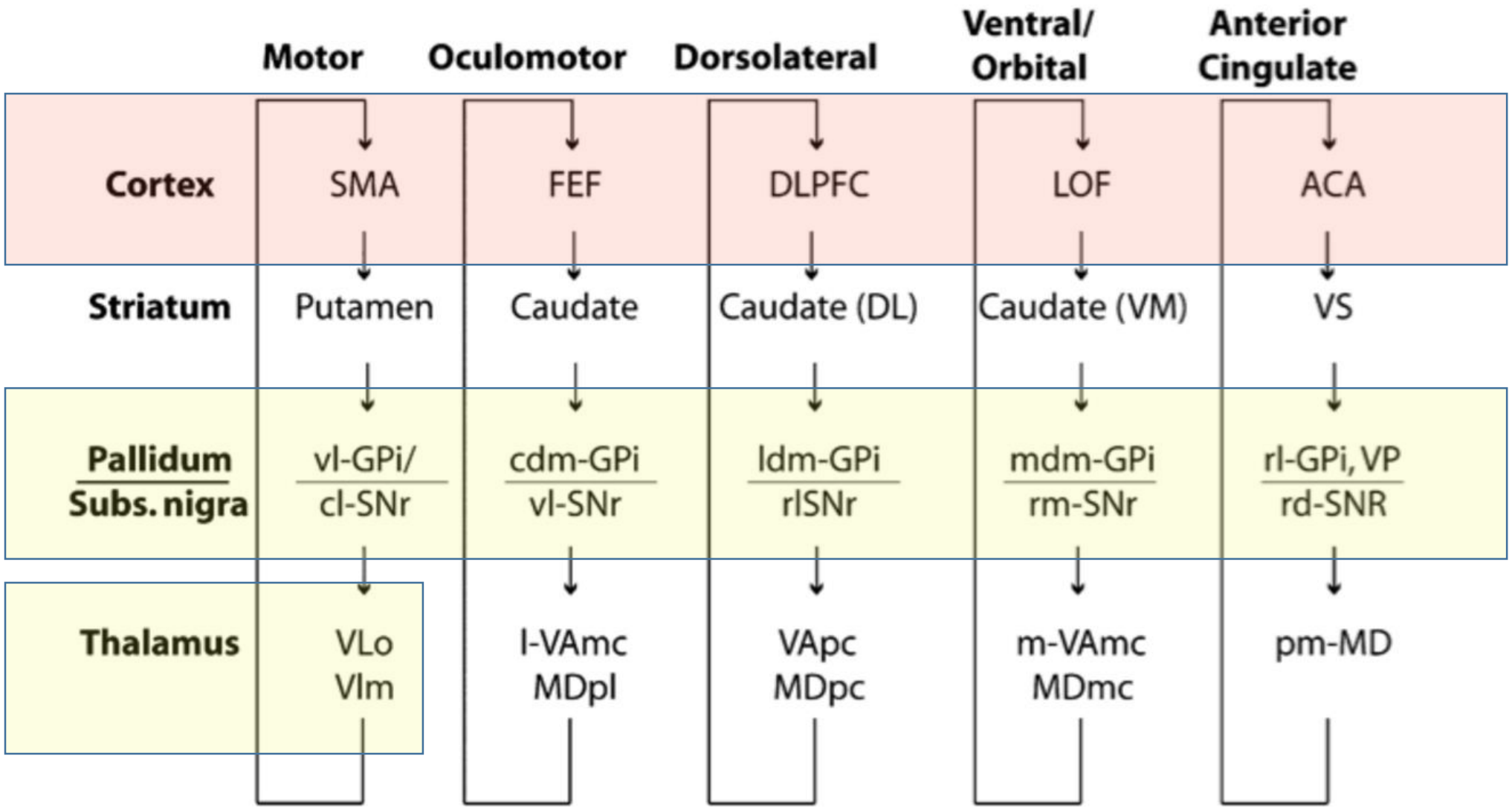
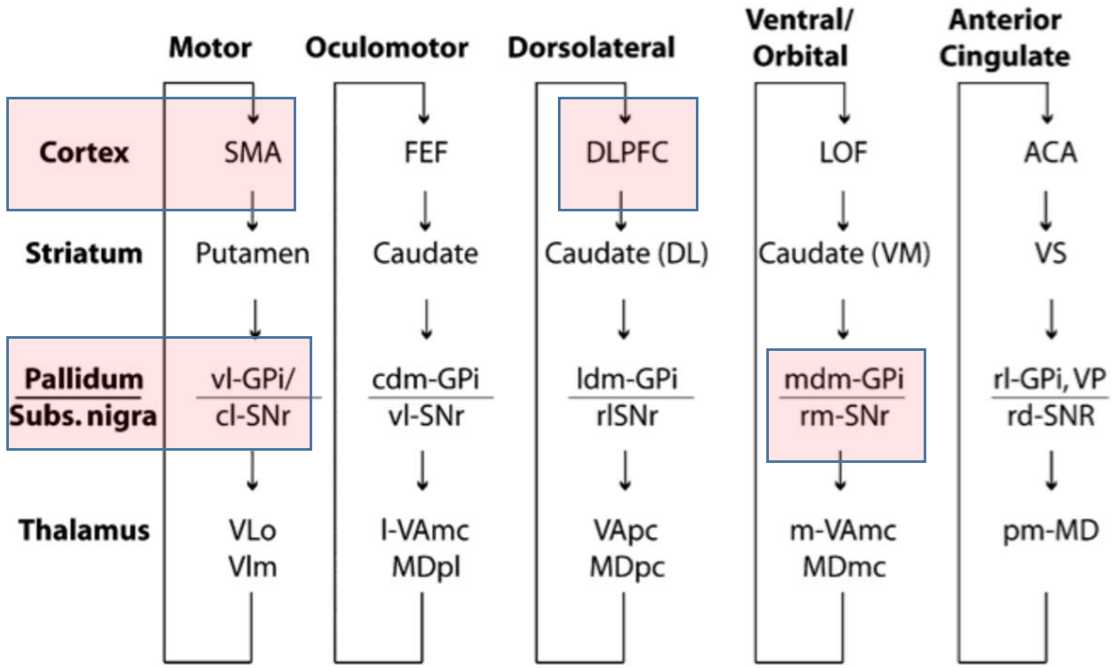
SNr: 2.41mm

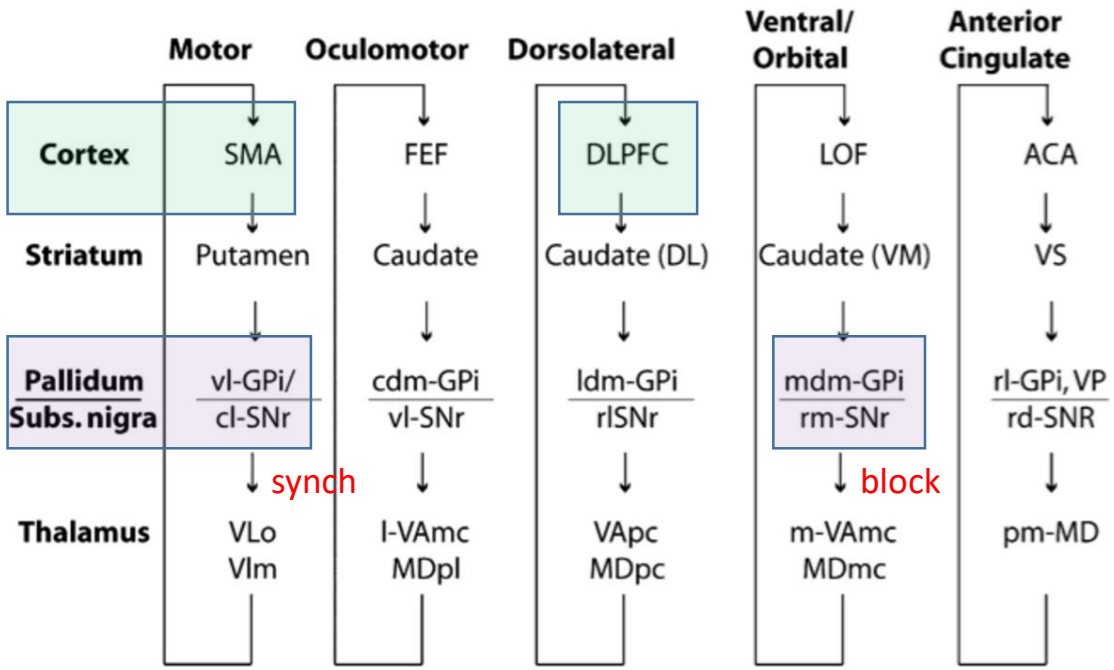

A
1.1 mm
Guide tube
210 mm
0.66 mm
Insulation
11.3 mm
Stimulation
electrode
1.4 mm
0.55 mm
150 µm
Recording
electrode
100 µm
25 µm
B
Guide tube
Insulation
12 mm ± D
2 mm
Stimulation
electrodes
C
(mm)
1.27
C3
C2
0.5
C1
1.5
C0


Motor
Oculomotor
Dorsolateral
Ventral/ Orbital
Anterior Cingulate
Cortex
SMA
FEF
DLPFC
LOF
ACA
Striatum
Putamen
Caudate
Caudate (DL)
Caudate (VM)
VS
Pallidum
Subs. nigra
vl-GPi/ cl-SNr
cdm-GPi vl-SNr
ldm-GPi rlSNr
mdm-GPi rm-SNr
rl-GPi, VP rd-SNR
Thalamus
VLo Vlm
l-VAmc MDpl
VApc MDpc
m-VAmc MDmc
pm-MD

Pathologic



Normalized Output



Functional Neurosurgery

- Probably the greatest opportunity to study and improve brain function in pathological circumstances.
- Methods are crude and guided by incomplete knowledge or guesses from primate models.
- Frontiers are real: movement disorders and other neurodegenerative diseases, psychiatry-behavior, obesity, X.
- Only setting in which human neuronal activity can be obtained in an ethically acceptable manner.
- Desperately need TOOLS to identify and define pathologic “state(s)” pre operatively (class of patients and individuals).

Is there a place for network physiological methods in neurosurgery?

- Abundant data – not clear how best to use it.
- **Can we do better** than **normalization of bedside physiologic parameters we can measure and wait?**
- Can we use the perspective of configurations and element coupling to define and visualize real and clinically relevant states of brain and brain-system? Can we create a more granular catalog of disease states?
- Can we use identified states to study clinical paths from COMA to recovery?
- Can we use a catalog definable states to select and alter anatomical targets in the human brain to treat disease or ameliorate its effects?