# Feeding the Penumbra by Collateral Enhancement

## Sphenopalatine Ganglion Stimulation, Induced Hypertension, Vasodilators, Other Strategies

Jeffrey L. Saver, MD. FAAN, FAHA

Director, UCLA Comprehensive Stroke and Vascular Neurology Program

SA Vice-Chair and Professor of Neurology, DGSOM

# JLS Disclosures

- Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.
- Unpaid site investigator in multicenter trials run by Medtronic, Stryker, and Lundbeck, for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
- Receives funding for services as a scientific consultant regarding trial design and conduct to BrainsGate, Medtronic/Covidien, Stryker, Neuravi, Rapid Medical, Pfizer, Boehringer Ingelheim (prevention only), and St. Jude Medical.
- Serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service.

# Collaterals and Los Angeles

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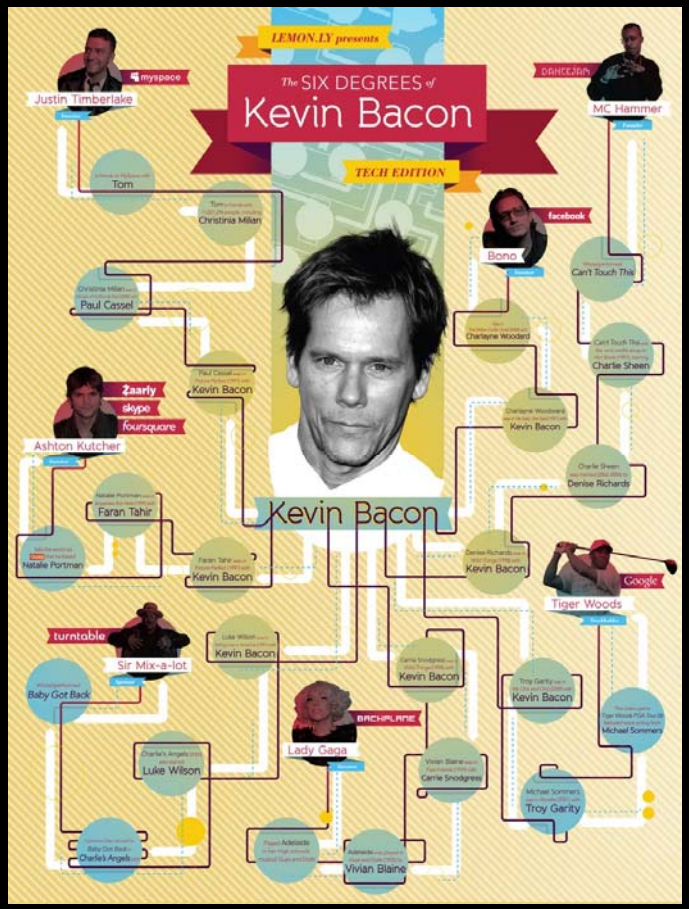
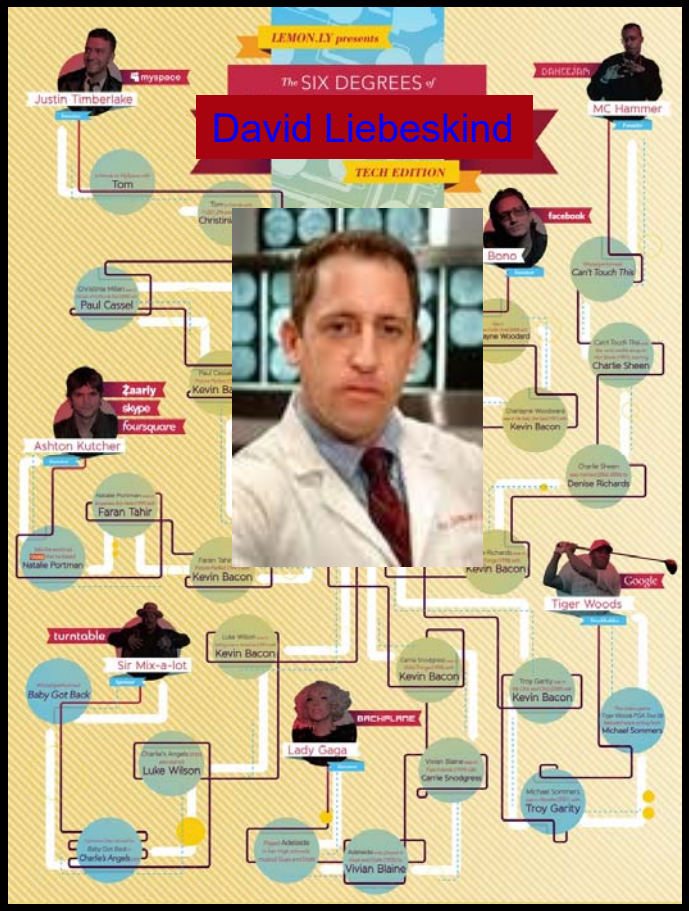


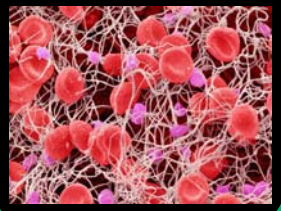
# Collaterals and Los Angeles



# Five Major Strategies to Treat Acute Ischemic Stroke

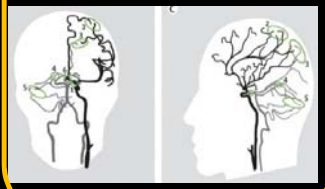
**Supportive Care**

**Avert Clot Propagation**

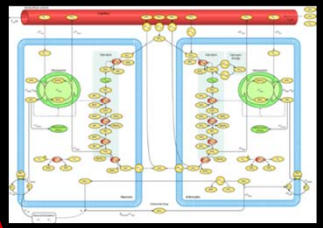


**Recanalization**


**Collateral Enhancement**



**Neuroprotection**



# Three Major Methodologies to Treat Acute Ischemic Stroke

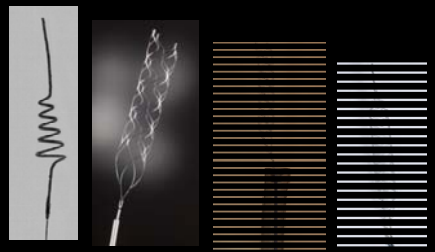
## Pharmacologic


Antiplatelet
1956 (LA)

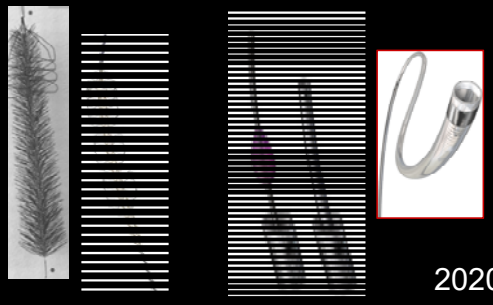

Thrombolytic
1995

Neuroprotective
?? (NA-1)

## Mechanical Endovascular



Coil Retriever
2004 (LA)



2020

## Neuromodulation

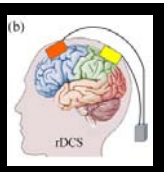
*Peripheral – Electrical + Magnetic*

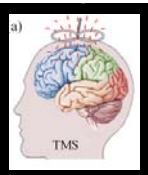
SPG Stim

Vagal N Stim

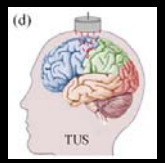
NME Stim

*Central - Electrical + Magnetic*




*Central - Ultrasound*




*UCLA Stroke Center*

# Two Broad Settings for Acute Collateral Enhancement Therapy

- Bridging therapy
  - » In patients on way to IVT and/or EVT recanalization treatment
- Destination therapy
  - » Patients
    - Ineligible for IVT and EVT
    - Who have failed IVT and EVT
  - » Reasons potentially still helpful
    - Can permanently increase perfusion
      - » Hydrodynamic pressure needed to open a vessel more than that needed to avert collapse of a vessel
    - Can bridge to late disease-mitigating physiology
      - » Spontaneous recanalization
      - » Collaterogenesis
      - » Neuronal resilience via ischemic perconditioning

# Frequency of Substantial Salvageable Penumbra in Thrombectomy-Ineligible AIS Patients

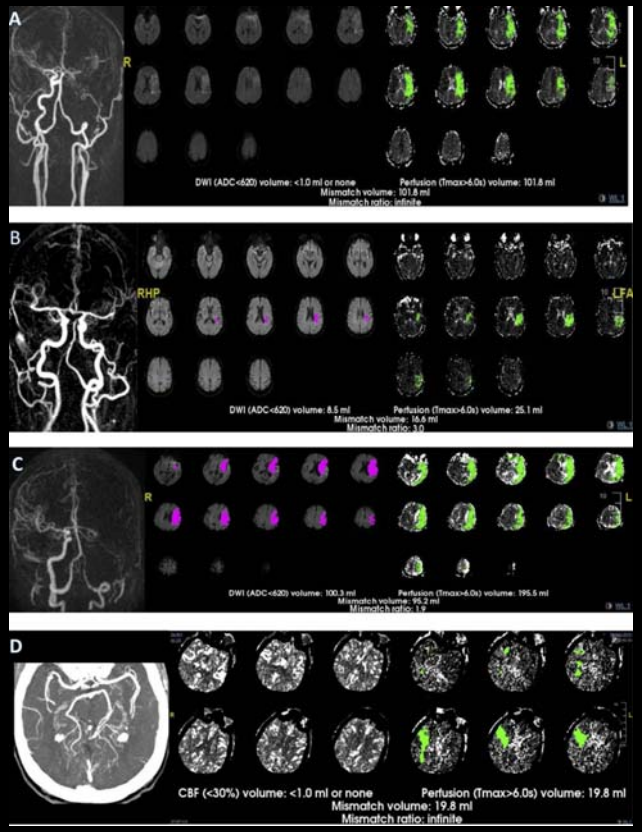
- 174 consecutive under-24h AIS patients
- 29 (17%) had LVO or MVO and substantial penumbra, but deemed ET ineligible
  - » 1 in 6 patients
- Mean age 81 45% female, median NIHSS 11
- Most common reasons
  - » Distal occlusion - 28%
  - » Mild deficit - 16%
  - » Large core – 13%
  - » Cervical ICA occlusion – 9%

*Chronic cervical ICA occlusion*

*Distal M2/M3 occlusion*

*Large core*

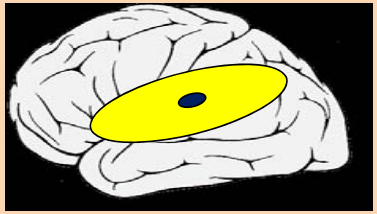
*Minimal deficit*

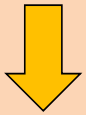



--Bahr Hosseini et al, J Neuroimag 2018

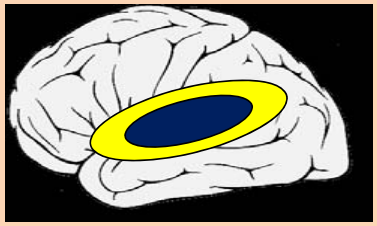
Standard Care

45 mins

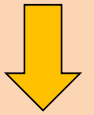




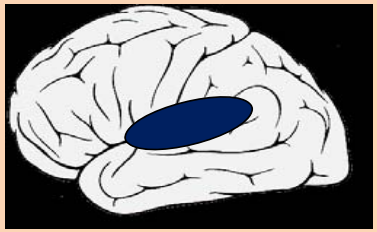
3 hours

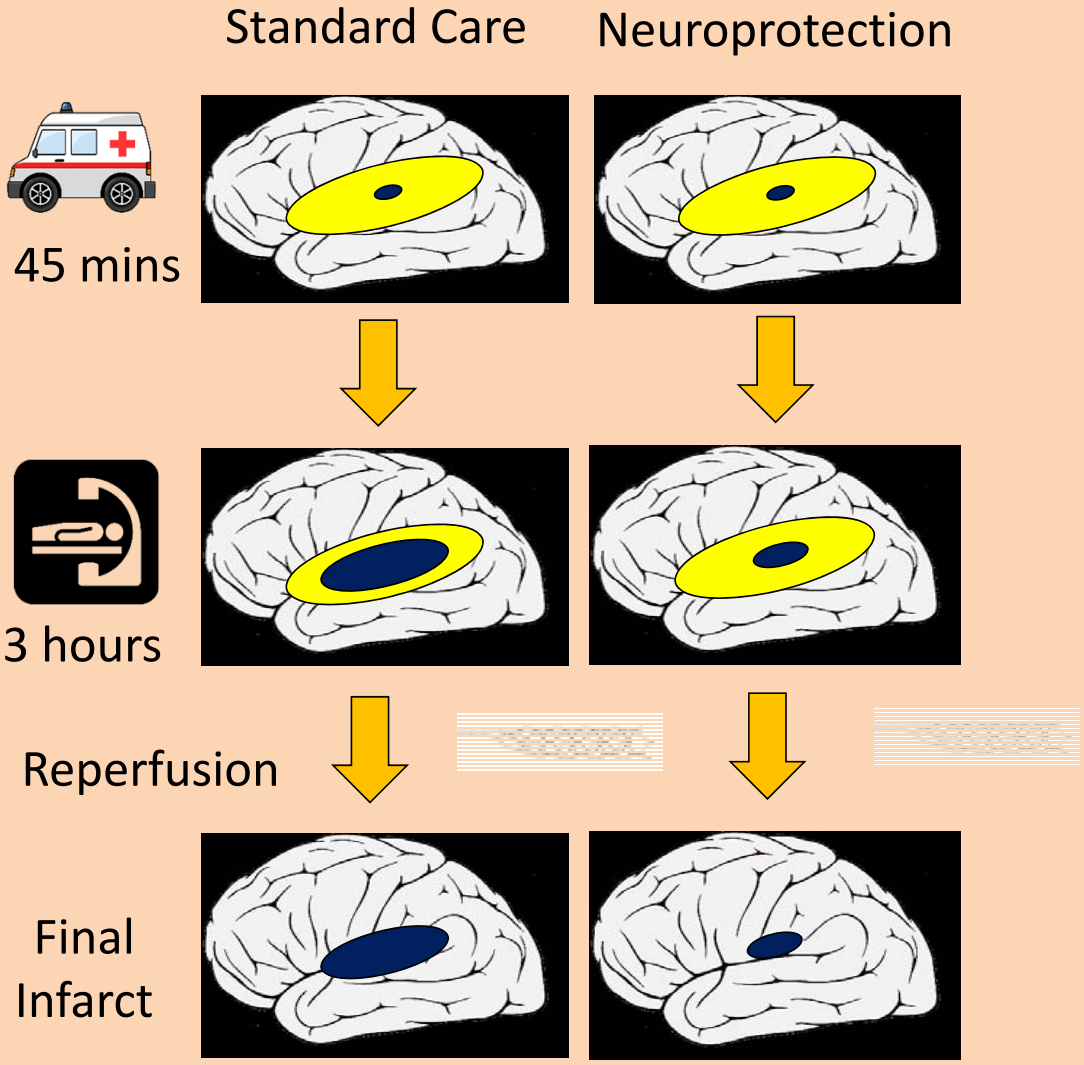


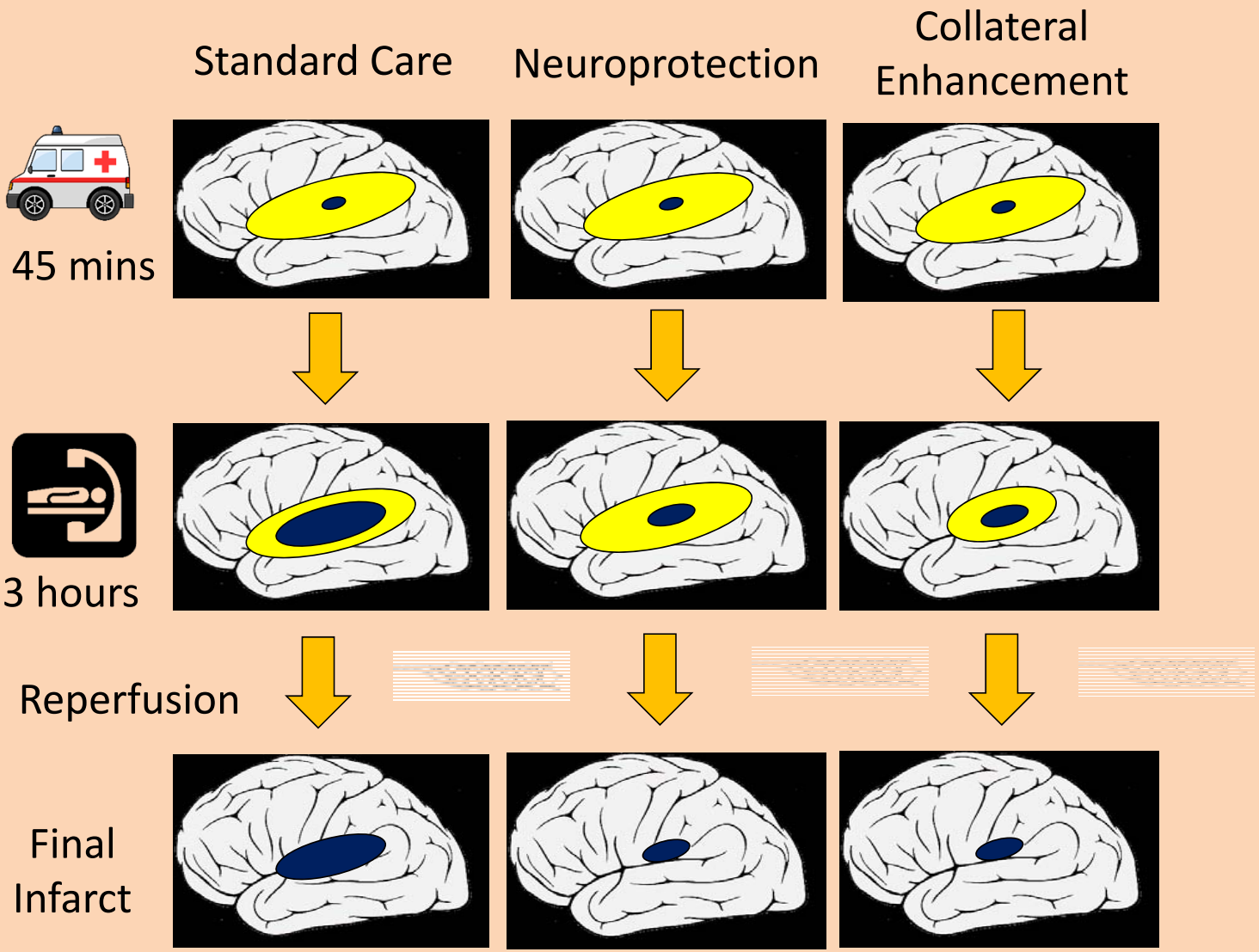
Reperfusion

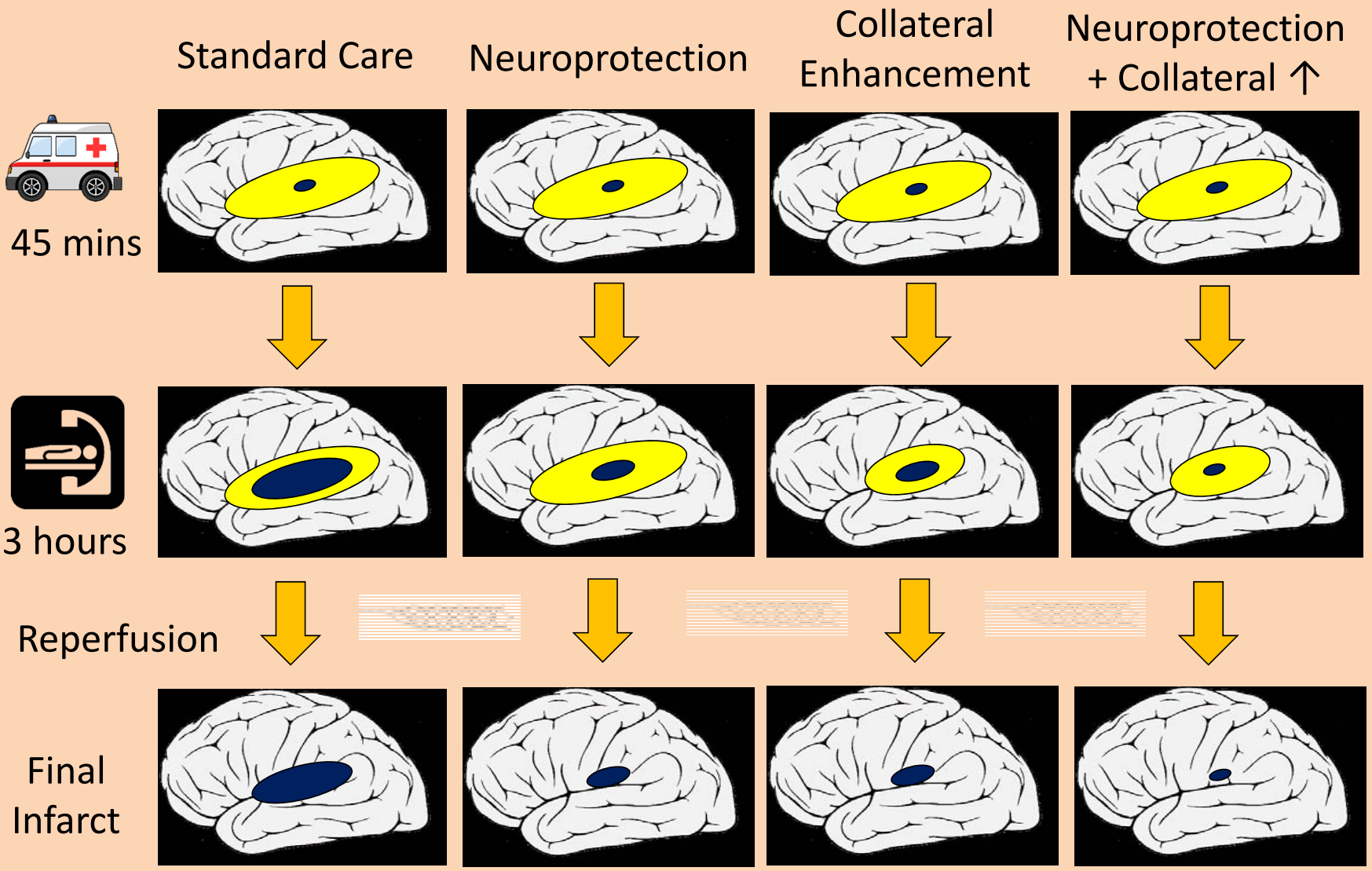


Final Infarct




Standard Care
Neuroprotection
45 mins
3 hours
Reperfusion
Final
Infarct

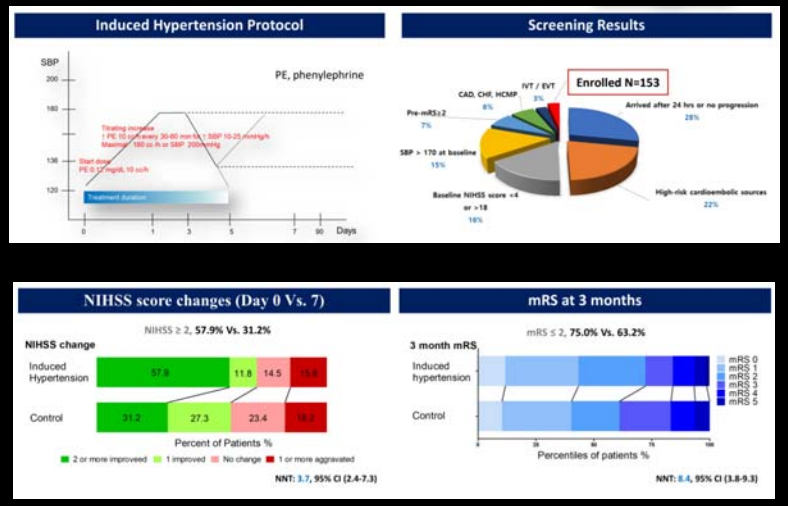

Standard Care
Neuroprotection
Collateral Enhancement
45 mins
3 hours
Reperfusion
Final Infarct


Standard Care
Neuroprotection
Collateral Enhancement
Neuroprotection + Collateral ↑
45 mins
3 hours
Reperfusion
Final Infarct

# Collateral Enhancement
# Old and New Tricks

## Induced HTN

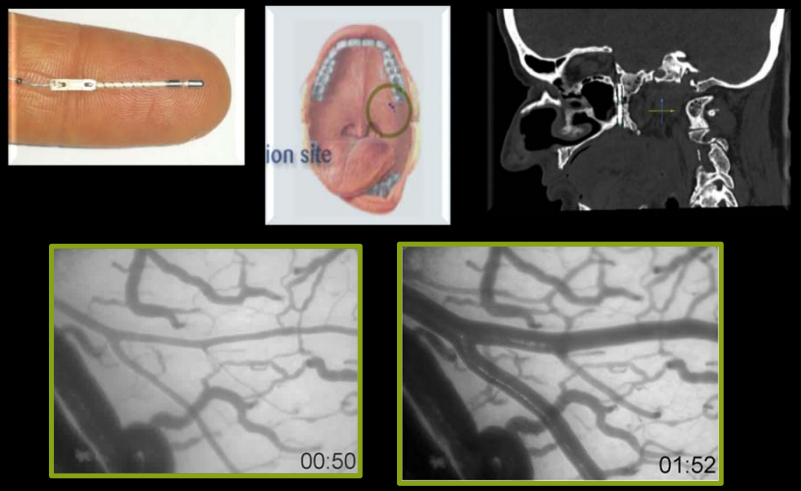
**SETIN Trial (n = 153)**




*--Bang et al, Neurology 2019*

## SPG Stimulation

**ImpACT 24B Trial (n = 1000)**

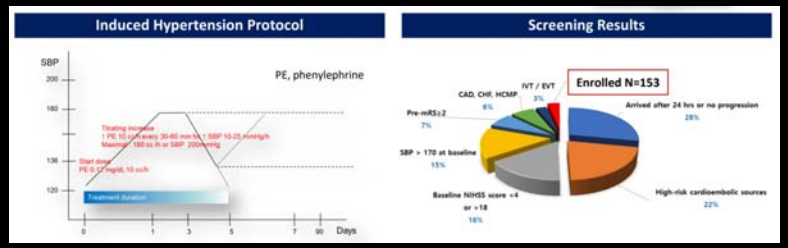


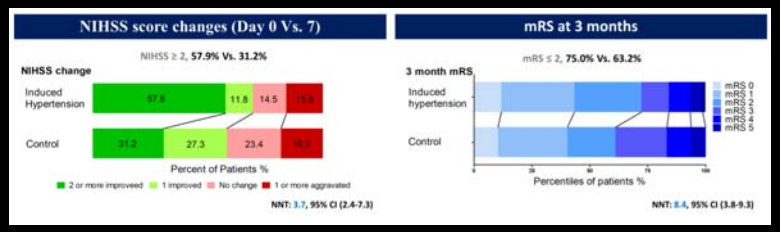

*--Bornstein, Saver, et al. Lancet 2019*

# Collateral Enhancement
# Old and New Tricks

**Induced HTN**

**SETIN Trial (n = 153)**

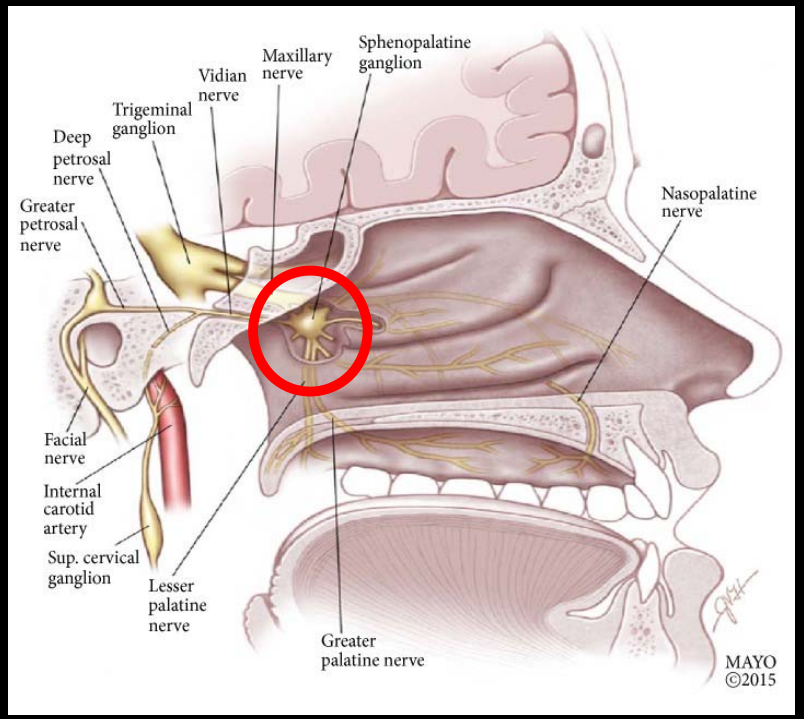



*--Bang et al, Neurology 2019*

# Sphenopalatine Ganglion

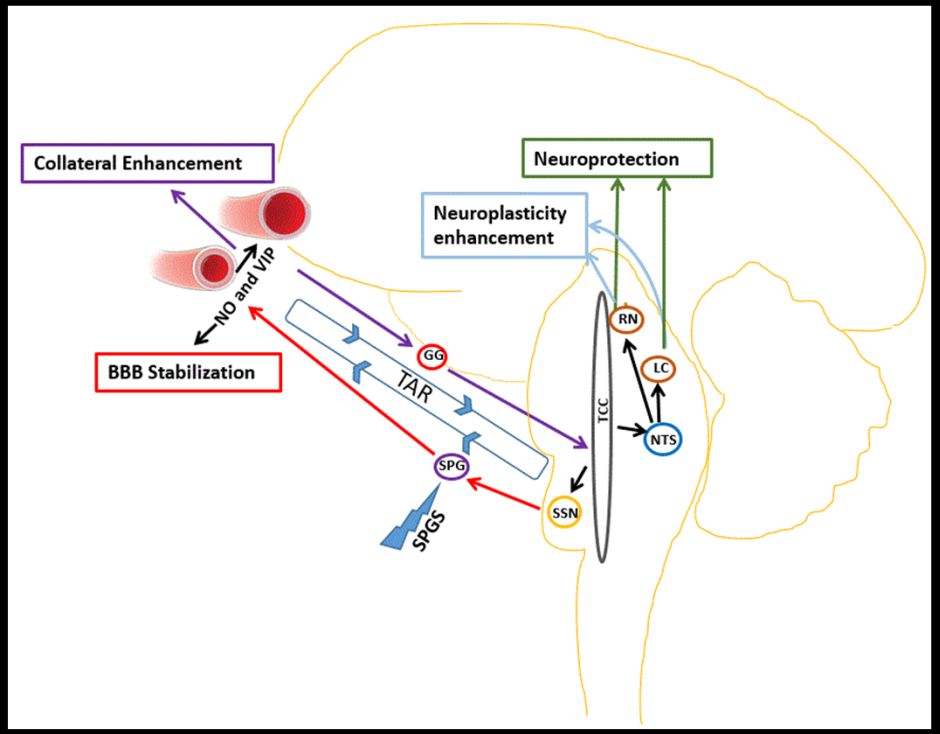
- Anatomy
  - » Pterygopalatine fossa
  - » Posterior to maxillary sinus
  - » 3mm, 60,000 nerve cells
- Componentts
  - » Parasympathetic synaptic cell bodies
  - » Traversing sympathetic and sensory
- Functions
  - » Dilation of anterior cerebral circulation
  - » Dilation of meningeal and dural vessels
  - » Scretomotor function to nasopharyngeal mucosaand lacrimal gland




*--Robbins et al, Headache 2016*

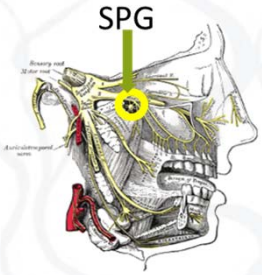
# SPG Stimulation as a Therapeutic Strategy for AIS

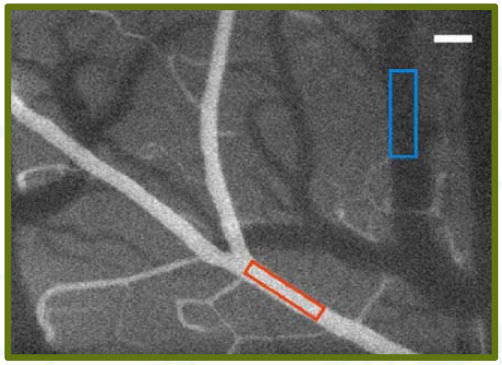
- Collateral enhancement
  - » Release of vasodilatory neurotransmitters (NO, ACH)
- Blood-brain barrier stabilization
  - » Reducing edema
- Neuroprotection
  - » Central cholinergic system activation
    - Anti-inflammatory, anti-apoptotic, anti-excitatory
- Neuroplasticity enhancement
  - » Central cholinergic and adrenergic neuromodulation of cortical networks
  - » NO release stimulating neurogenesis

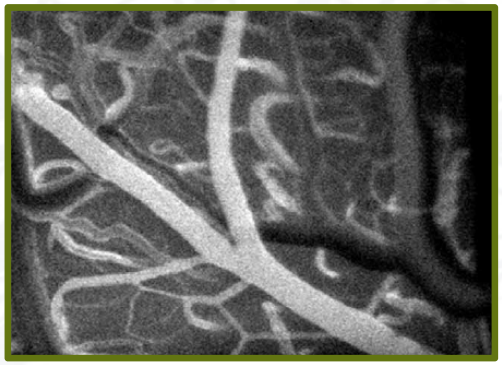



*--Bahr-Hosseini and Saver, submitted*

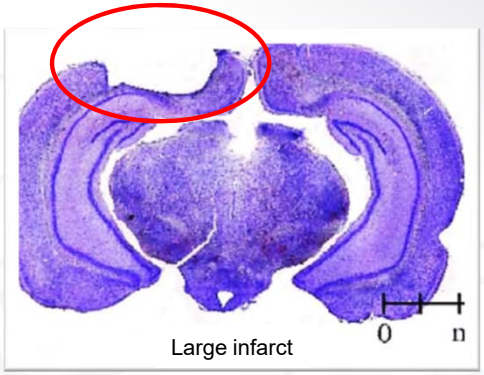
# SPG Stimulation – Collateral Enhancement, Infarct Reduction, BBB Preservation

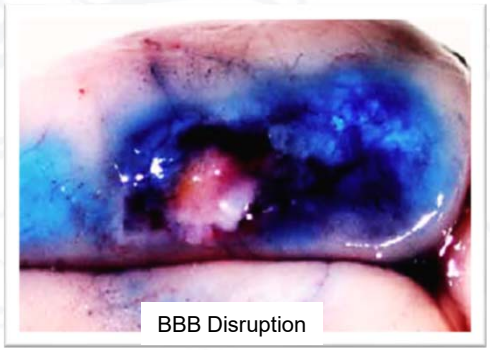


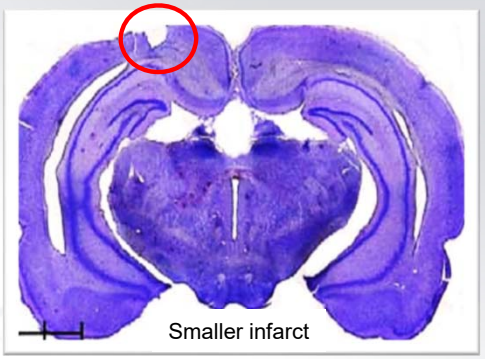


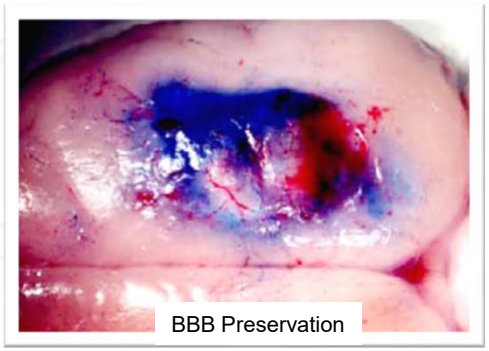
Control



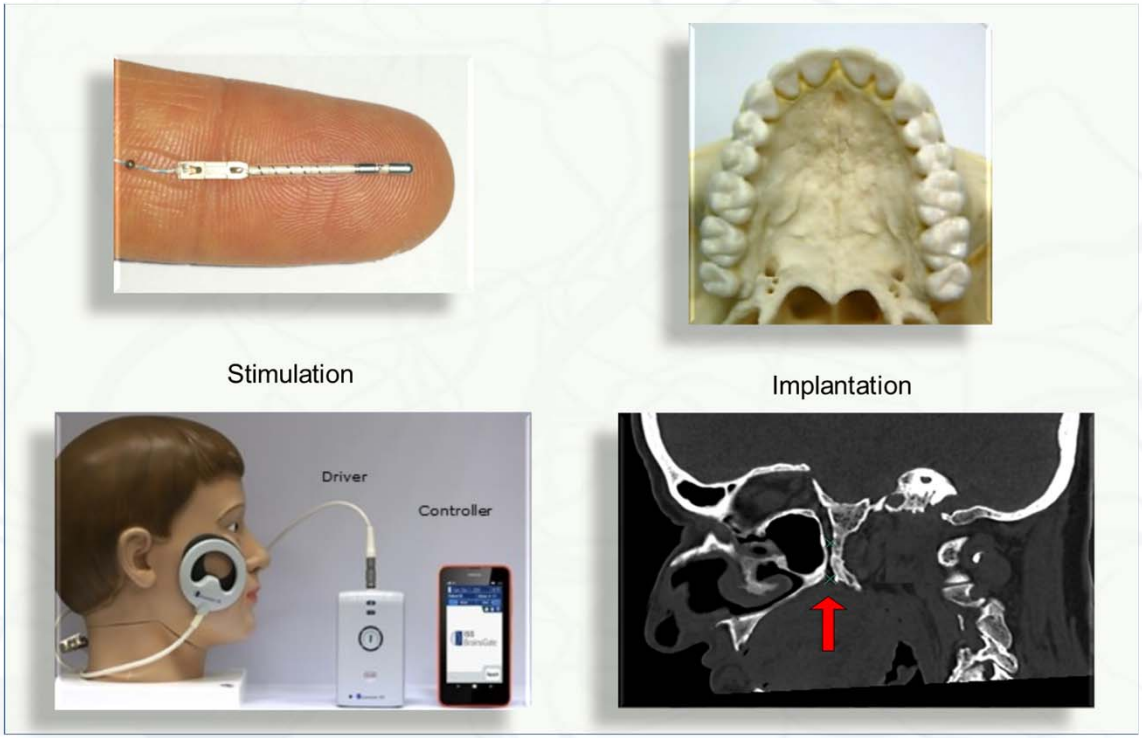

SPG Stimulation

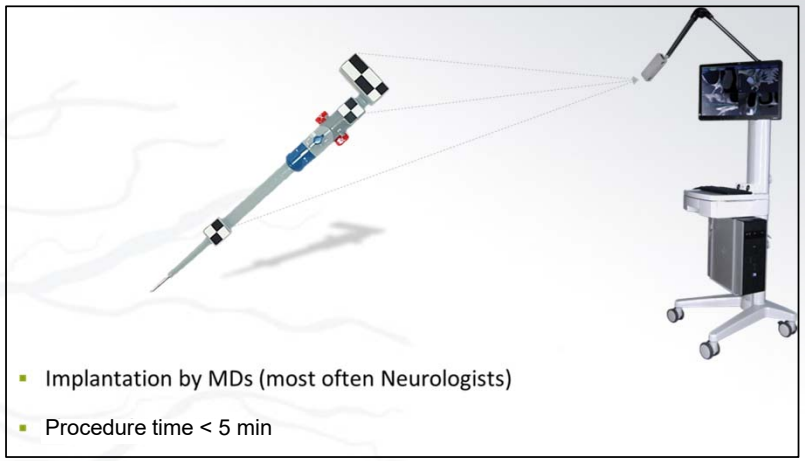



*Levi H, et al. Plos One 2012*

# Injectable Neuro Stimulation System (INSS)



- Implantation by MDs (most often Neurologists)
- Procedure time < 5 min

# The Implant for Augmentation of Cerebral Blood Flow Trials (ImpACT) Program

| Trial | Aim | Design | Size | Endpoint(s) |
|---|---|---|---|---|
| ImpACT-1 | Feasibility | Single-arm ≤24h, NIHSS 7-20 | 98 | Rx completion, SAEs |
| ImpACT-24A | Signals of efficacy, safety | Randomized 8-24h, NIHSS 8-24 | 253 | Favorable mRS at 3m |
| ImpACT-24B | Pivotal efficacy, safety | Randomized 8-24h, NIHSS 8-24 | 1000 | Favorable mRS at 3m |
| ImpACT-24M | Refinement + Explanatory | Single-arm ≤24h, NIHSS 1-5 | 50 | CCA Flow, Hand strength |
| ImpACT-P | Expansion + Explanatory | Randomized ≤8h, NIHSS ≥10 | 100 | Preserved tissue |

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| ImpACT-24B | Pivotal efficacy, safety | Randomized 8-24h, NIHSS 8-24 | 1000 | Favorable mRS at 3m | Lancet, 2019 |
| ImpACT-24M | Refinement + Explanatory | Single-arm ≤24h, NIHSS 1-5 | 50 | CCA Flow, Hand strength | Stroke, 2019 |
| ImpACT-P | Expansion + Explanatory | Randomized ≤8h, NIHSS ≥10 | 100 | Preserved tissue | Recruiting |

# The Implant for Augmentation o
# Blood Flow Trials (ImpACT) P

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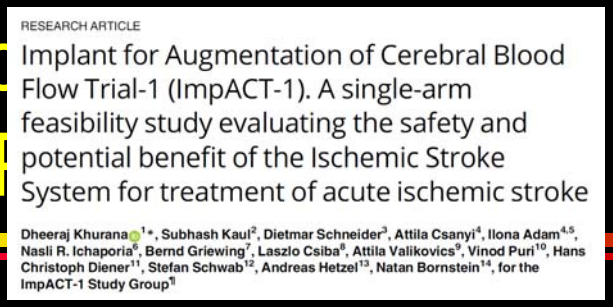
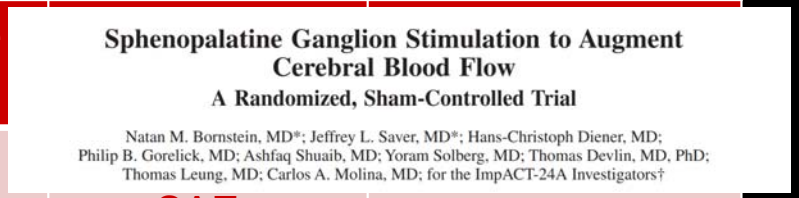
| ImpACT-P | Expansion + Explanatory | Randomized ≤8h, NIHSS ≥10 | 10 |


RESEARCH ARTICLE

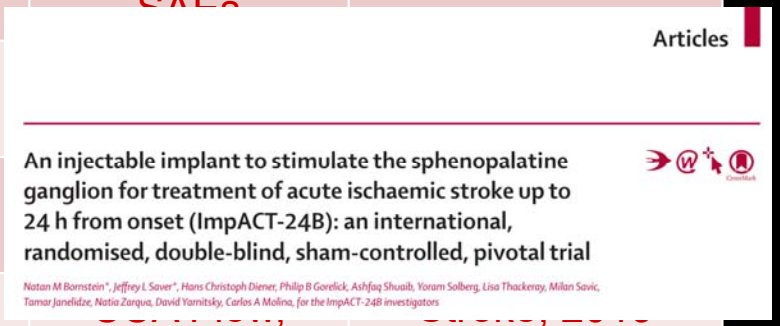
Implant for Augmentation of Cerebral Blood Flow Trial-1 (ImpACT-1). A single-arm feasibility study evaluating the safety and potential benefit of the Ischemic Stroke System for treatment of acute ischemic stroke

Dheeraj Khurana[1]*, Subhash Kaul[2], Dietmar Schneider[3], Attila Csanyi[4], Ilona Adam[4,5], Nasli R. Ichaporia[6], Bernd Griewing[7], Laszlo Csiba[8], Attila Valikovics[9], Vinod Puri[10], Hans Christoph Diener[11], Stefan Schwab[12], Andreas Hetzel[13], Natan Bornstein[14], for the ImpACT-1 Study Group[¶]


Sphenopalatine Ganglion Stimulation to Augment Cerebral Blood Flow

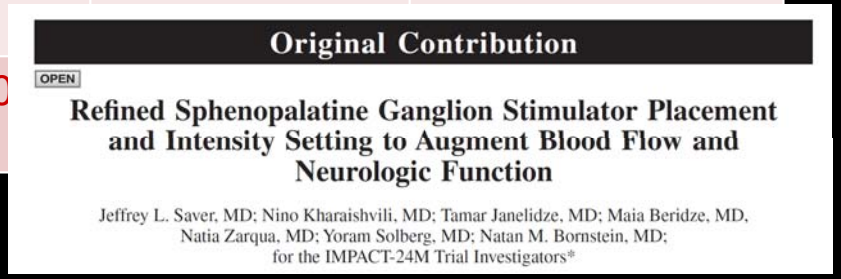
A Randomized, Sham-Controlled Trial

Natan M. Bornstein, MD*; Jeffrey L. Saver, MD*; Hans-Christoph Diener, MD; Philip B. Gorelick, MD; Ashfaq Shuaib, MD; Yoram Solberg, MD; Thomas Devlin, MD, PhD; Thomas Leung, MD; Carlos A. Molina, MD; for the ImpACT-24A Investigators†


Articles

An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial

Natan M Bornstein*, Jeffrey L Saver*, Hans Christoph Diener, Philip B Gorelick, Ashfaq Shuaib, Yoram Solberg, Lisa Thackeray, Milan Savic, Tamar Janelidze, Natia Zarqua, David Yarnitsky, Carlos A Molina, for the ImpACT-24B investigators


Original Contribution

OPEN

Refined Sphenopalatine Ganglion Stimulator Placement and Intensity Setting to Augment Blood Flow and Neurologic Function

Jeffrey L. Saver, MD; Nino Kharaishvili, MD; Tamar Janelidze, MD; Maia Beridze, MD, Natia Zarqua, MD; Yoram Solberg, MD; Natan M. Bornstein, MD; for the IMPACT-24M Trial Investigators*

# Sphenopalatine Ganglion Stimulation

# Improves Outcome from Acute Ischemic Stroke in a Dose-Dependent Manner:

# Further Insights from the Pivotal ImpACT-24B Trial

JL Saver, NM Bornstein, H-C Diener, PB Gorelick, T Janelidze, M Savic, N Zarqua, A Shuaib, D Yarnitsky, CA Molina

for the ImpACT-24B Trial Investigators

# ImpACT-24B Pivotal Trial

| | Study Design |
|---|---|
| Objective | Safety & efficacy in anterior circulation stroke in 8-24hr window, NIHSS 7-18 |
| Design | Randomized, Double-Blind, Sham-Controlled |
| Primary Endpoint | mRS improvement beyond expectations at 3 months (sliding dichotomy) |
| Two Primary Analysis Populations | • mITT – all patients receiving at least one active/sham SPG stimulation<br>• Confirmed Cortical Involvement (CCI) - NIHSS ≥ 10, at least one cortical ASPECTS region |
| Multiplicity Adjustment | Hochberg multistep procedure*: requires $p<0.05$ in both populations, or $p<0.025$ in one |
| Sample Size | Between 450 -1000 (prespecified sample size adjustment rule at interim analysis of 350 patients) |
| Enrollment | 18 countries, 73 sites, 1,000 mITT patients, June 2011 – March 2018 |

**Hochberg Y. Biometrika 1988;75:800-802 / Multiple Endpoints in Clinical Trials: FDA Draft Guidance, 2017 / Lees KR et al. ESOC 2018:AS02-011*

# Key Inclusion / Exclusion Criteria

| Inc. Criteria | Range |
|---|---|
| Age | M 40 – 80<br>F 40 – 85 |
| NIHSS | 7 - 18 |
| TFSO | 8 – 24h |
| Clinical & Radiological | Anterior circulation |

| Exc. Criteria | Feature |
|---|---|
| Imaging | • ICH<br>• Massive (>2/3)<br>• Lacunar<br>• Posterior circulation |
| Reperfusion Therapy | • IV thrombolysis<br>• EVT |

# ImpACT-24B Study Flow

| Time Period | Activity |
|---|---|
| Day 1 | • 1:1 dynamic randomization<br>• Neurostimulator / Sham implantation<br>• 1st SPG / Sham stimulation 4h |
| Days 2-5 | • Daily SPG / Sham stimulation 4h<br>• Implant / Sham removal<br>• Day 5 mRS, NIHSS |
| Follow Up | • Day 30, 60 mRS, NIHSS<br>• Day 90 mRS, NIHSS, SIS-16<br>  • mRS – Local blinded and centrally reviewed |

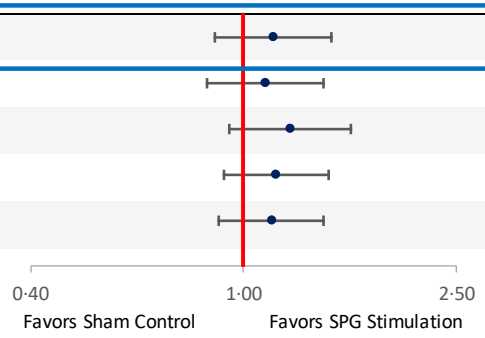
# Patient Features

| | mITT Population | | CCI Population | |
|---|---|---|---|---|
| | Treated | Sham | Treated | Sham |
| N | 481 | 519 | 244 | 276 |
| Age, years | 70 | 71 | 70 | 72 |
| Sex (female) | 50% | 52% | 48% | 49% |
| NIHSS | 12 (9 - 14) | 12 (9 - 14) | 13 (12 - 15) | 13 (11 - 15) |
| Stroke side (left brain) | 57% | 50% | 57% | 52% |
| Pre-stroke mRS > 0 | 8·5% | 5·6% | 8·6% | 6·2% |
| Hypertension | 87% | 84% | 87% | 85% |
| Diabetes | 24% | 27% | 22% | 24% |
| Atrial Fibrillation | 25% | 26% | 34% | 31% |
| ASPECTS | 8 (6 - 9) | 8 (6 - 9) | 7 (5 - 8) | 7 (5 - 8) |
| Onset (LKW) to 1st Tx | 19·9 (16·0 - 22·6) | 18·7 (15·6 - 21·8) | 19·7 (15·8 - 22·5) | 18·5 (15·5 - 21·1) |

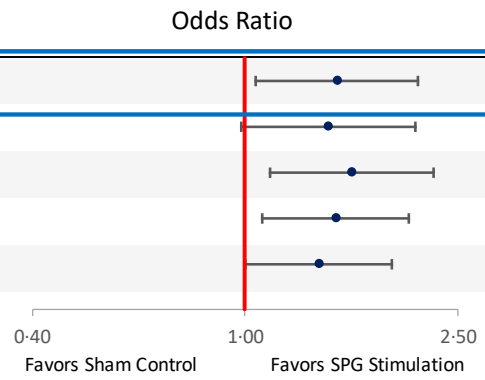
*Time from LKW (Implantation longer than Sham) p<0.0001; mITT: Side randomization imbalance p=0.04; CCI: No other differences with p<0.1*

# Efficacy Results –ImpACT-24B

| mITT | SPG Stimulation | Sham Control | Odds Ratio | Odds Ratio | P Value |
|---|---|---|---|---|---|
| Sliding Dichotomy | 48·6% | 45·5% | 1·14 [0·89, 1·46] | | 0·31 |
| Dichotomy 0-2 | 44·1% | 41·8% | 1·10 [0·85, 1·41] | | 0·47 |
| Dichotomy 0-3 | 67·6% | 63·0% | 1·22 [0·94, 1·59] | | 0·13 |
| SIS-16 | 57·7 | 54·7 | 1·15 [0·92, 1·44] | | 0·23 |
| Utility weighted mRS | 55·83 | 53·18 | 1·13 [0·90, 1·41] | | 0·24 |




| CCI | SPG Stimulation | Sham Control | Odds Ratio | Odds Ratio | P Value |
|---|---|---|---|---|---|
| Sliding Dichotomy | 49·6% | 39·9% | 1·48 [1·05, 2·10] | | 0·0258 |
| Dichotomy 0-2 | 34·8% | 27·2% | 1·43 [0·99, 2·08] | | 0·06 |
| Dichotomy 0-3 | 62·3% | 51·1% | 1·58 [1·11, 2·25] | | 0·01 |
| SIS-16 | 52·2 | 43·9 | 1·48 [1·08, 2·02] | | 0·01 |
| Utility weighted mRS | 50·00 | 43·89 | 1·37 [1·00, 1·87] | | 0·05 |



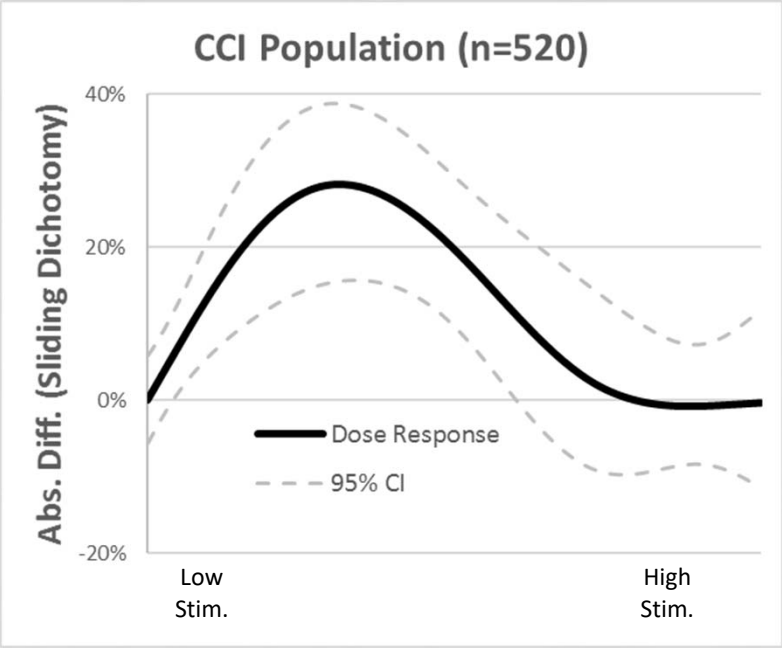
# Efficacy Results – Pooled ImpACT-24A + 24B Trials (IPD Meta-Analysis)

| **mITT** | Treated | Control | Odds Ratio | CI | P-value |
|---|---|---|---|---|---|
| 24A (n=253) | 49.7% | 40.0% | 1.48 | (0.89-2.47) | 0.13 |
| 24B (n=1000) | 48.6% | 45.5% | 1.14 | (0.89 - 1.46) | 0.31 |
| Pooled (n=1253) | 48.9% | 44.6% | 1.20 | (0.96 – 1.49) | 0.12 |

| **CCI** | Treated | Control | Odds Ratio | CI | P-value |
|---|---|---|---|---|---|
| 24A (n=87) | 50.0% | 27.0% | 2.70 | (1.08-6.73) | 0.03 |
| 24B (n=1000) | 49.6% | 39.9% | 1.48 | (1.05 - 2.10) | 0.0258 |
| **Pooled (n=607)** | **49.7%** | **38.3%** | **1.61** | **(1.16-2.13)** | **0.004** |

*--Shuaib A, et al. ISC 2019*

# Relation Between Stimulation Level and Clinical Outcomes

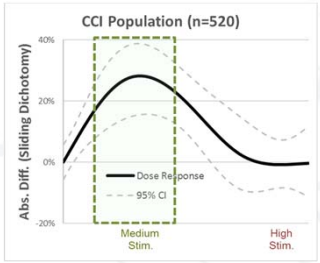



| Endpoint* | Dose Response p-value |
|---|---|
| Favorable Outcome (mRS Sliding Dichotomy) | 0.003 |
| Independence (mRS 0-2) | 0.02 |
| Self-Care or Better (mRS 0-3) | 0.01 |
| Stroke-Related QOL (SIS-16) | 0.03 |
| Disability level (UW-mRS) | 0.03 |

*Adjusted for: age, sex, NIHSS, side, ASPECTS, OTT, DM, AF, and predicted mRS mean-median difference

- Inverted U-Shaped Dose Effect Curve (IUSDEC)

# ImpACT-24B Efficacy in Optimal Dose Range (1%-38% of Max Dose)




| Outcome | SPG stim (N=61) | Sham stim (N=276) | Odds ratio (95% CI) | p-value |
|---|---|---|---|---|
| Favorable Outcome (mRS Sliding Dichotomy) | 68·9% | 39·9% | 3·34 (1·84-6·04) | <0·0001 |
| Independence (mRS 0-2) | 54·1% | 27·2% | 3·16 (1·79-5·58) | <0·0001 |
| Self-Care or Better (mRS 0-3) | 82·0% | 51·1% | 4·35 (2·17-8·71) | <0·0001 |
| | SPG stim (N=61) | Sham stim (N=276) | Diff. (95% CI) | p-value |
| Stroke-Related QoL (SIS-16) | 67·3 | 43·9 | 23·5 (12·7-34·2) | <0·0001 |
| Disability level (UW-mRS) | 64·6 | 43·9 | 20·7 (10·8-30·6) | <0·0001 |

## Lancet Publication


**May 24, 2019**

**An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial**

*Natan M Bornstein*, Jeffrey L Saver*, Hans Christoph Diener, Philip B Gorelick, Ashfaq Shuaib, Yoram Solberg, Lisa Thackeray, Milan Savic, Tamar Janelidze, Natia Zarqua, David Yarnitsky, Carlos A Molina, for the ImpACT-24B investigators*

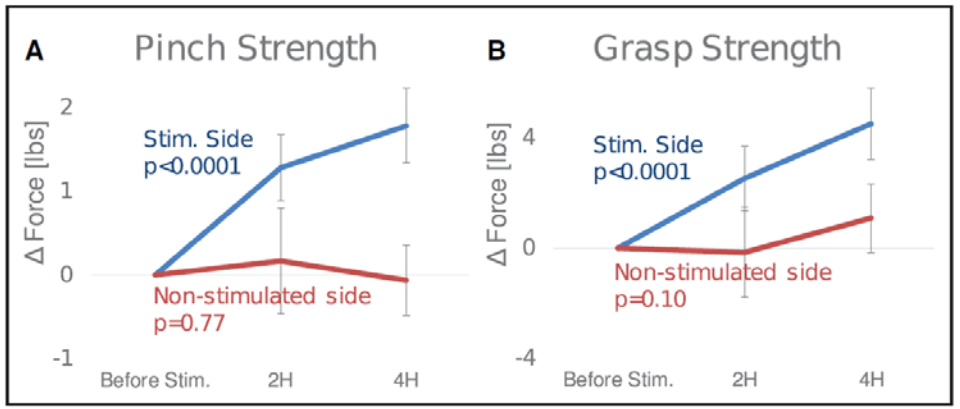
"The cumulative evidence indicates that, for patients with confirmed cortical ischemia 8-24h after onset, SPG stimulation reduces post-stroke disability over the entire outcome range and increases the proportion of patients alive and independent 3 months after stroke."

# ImpACT-24M SPG Stim In-Session Effects on Blood Flow and Neural Function

## Cervicocranial Flow - CCA

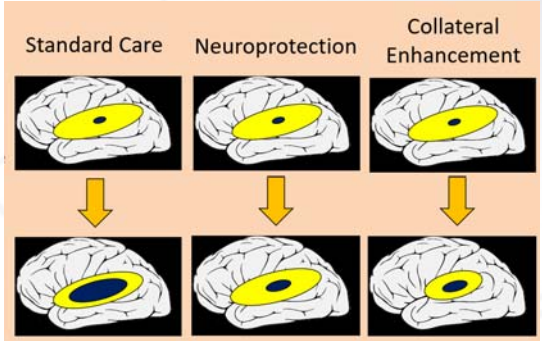
| | BL | Stim | Change | p |
|---|---|---|---|---|
| Diameter (mm) | 8.0 | 8.9 | ↑11% | <0.0001 |
| Velocity (PS,cm/s) | 66 | 77 | ↑17% | 0.0001 |
| Flow (PS,cm/s) | 33 | 47 | ↑44% | <0.0001 |

## Hand Strength




*--Saver JL, et al. Stroke 2019*

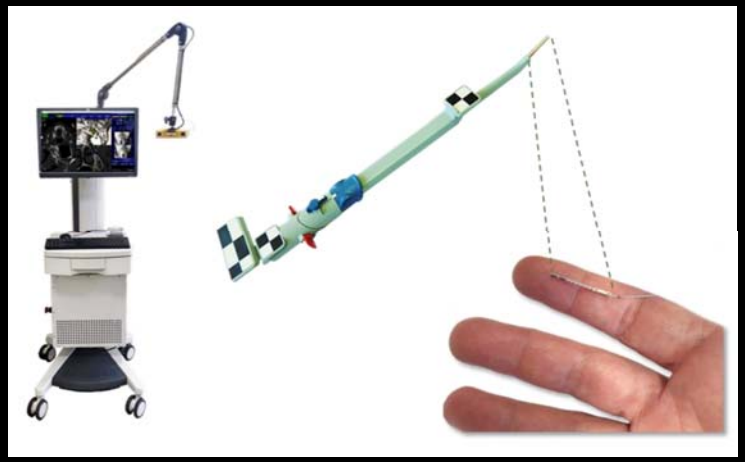
# ImpACT-P - IMPlant Augmenting Cerebral Blood Flow to Preserve the Penumbra Trial

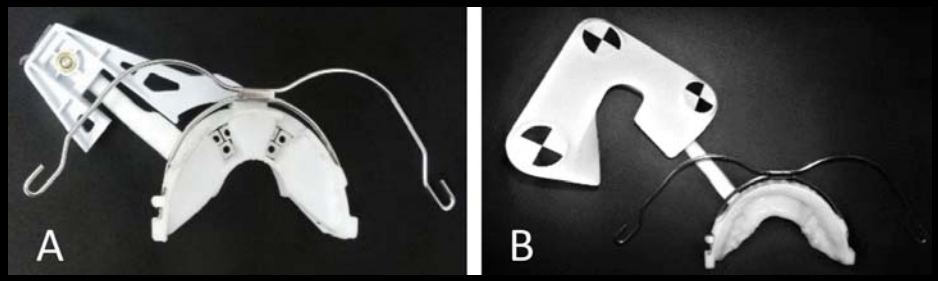



| | Study Design |
|---|---|
| Objective | Preservation of ischemic tissue |
| Design | Randomized, Double-Blind, Sham-Controlled |
| Lead Population | Anterior circulation LVO within 8h, with substantial penumbra on imaging |
| Primary Endpoint | Preserved tissue at 6h treatment, comprised of:<br>1) Penumbra freeze (Core volume growth/reduction)<br>2. Penumbra squeeze (Perfusion lesion volume growth/reduction) |
| Sample Size | 150 patients |
| Enrollment | 2 countries, 6 sites, 1st enrollment Oct 2019 |

# ImpACT Update

- Regulatory Status
  - » FDA
    - Clearance request being submitted
  - » EMA
    - CE mark for updated device being submitted
- Potential clinical availability
  - » 6-18 months





# I ate

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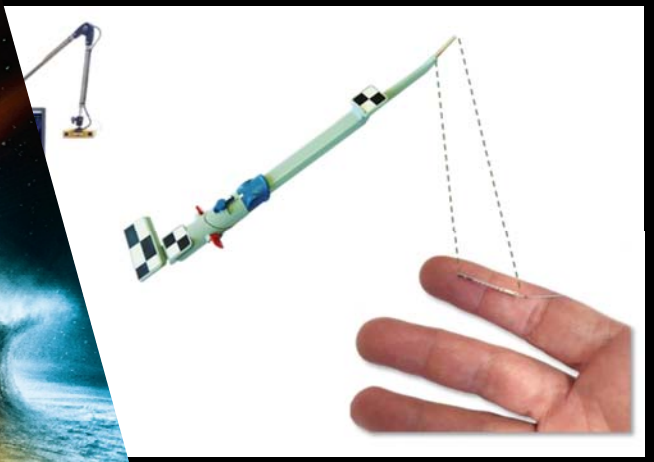
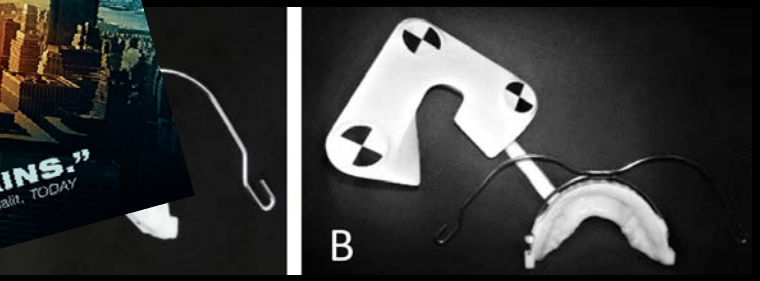
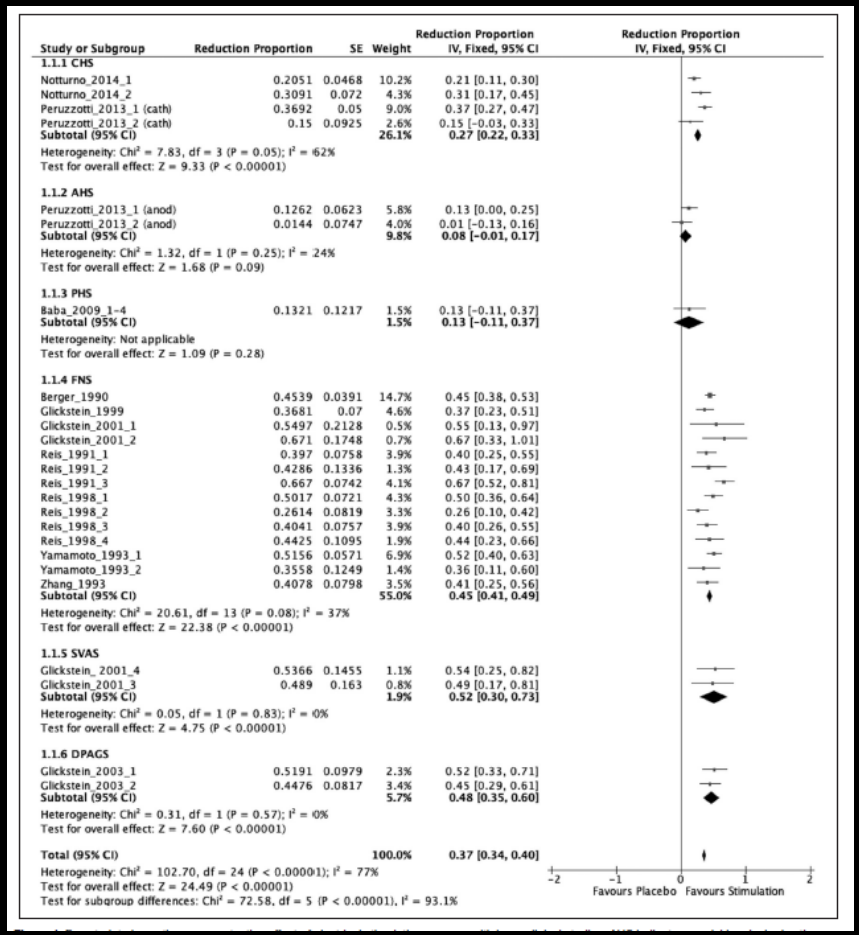




# CNS Transcranial and Direct Electrical Stimulation for Acute Neuroprotection – Preclinical Meta-Analysis

- Stimulation strategies - 6
  - » Transdural targeting ischemic zone
    - Cathodal hemispheric stimulation
    - Anodal hemispheric stimulation
    - Pulsed hemispheric stimulation
  - » DBS remote from ischemic zone
    - Fastigial nucleus
    - Subthalamic vasodilator area
    - Dorsal periaqueductal gray
- Overall, 28 experiments in 21 studies
  - » 350 animals
  - » Among the within-ischemic zone strategies
    - CHS reduced infarct volume, 27 %; 95% CI, 22%–33%; *P*<0.001
  - » Among the remote-from ischemic zone approaches
    - All (FNS, SVDA, DPG) reduced infarct volumes by half




*--Bahr-Hosseini et al, Stroke 2019*

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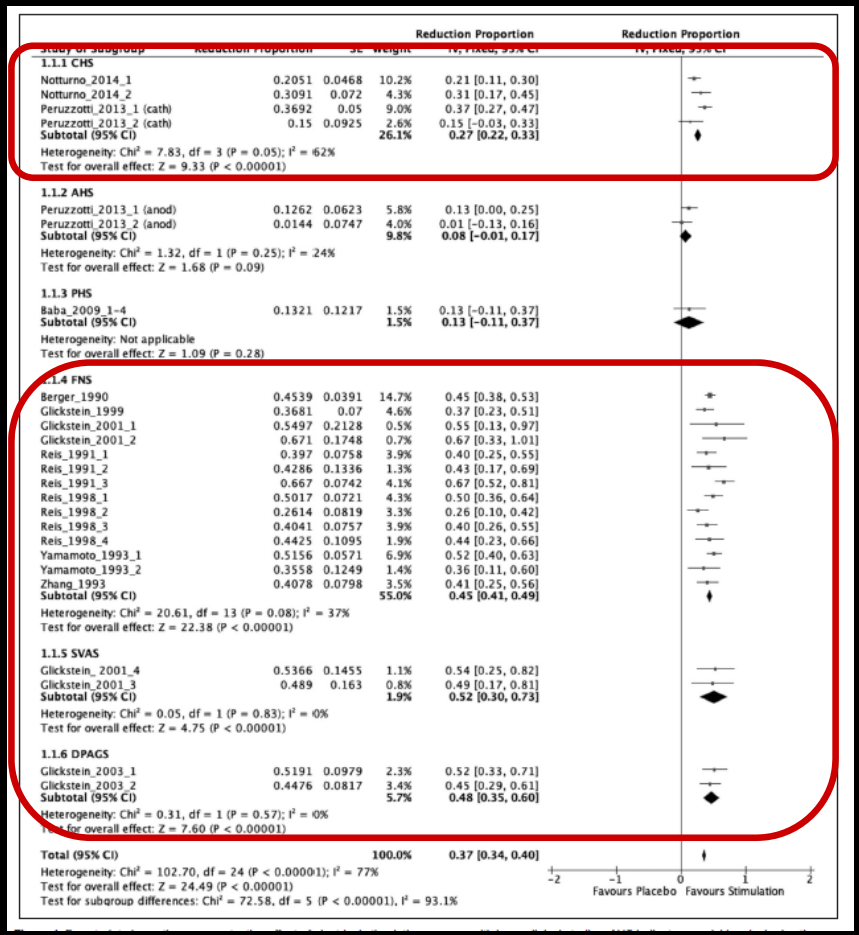
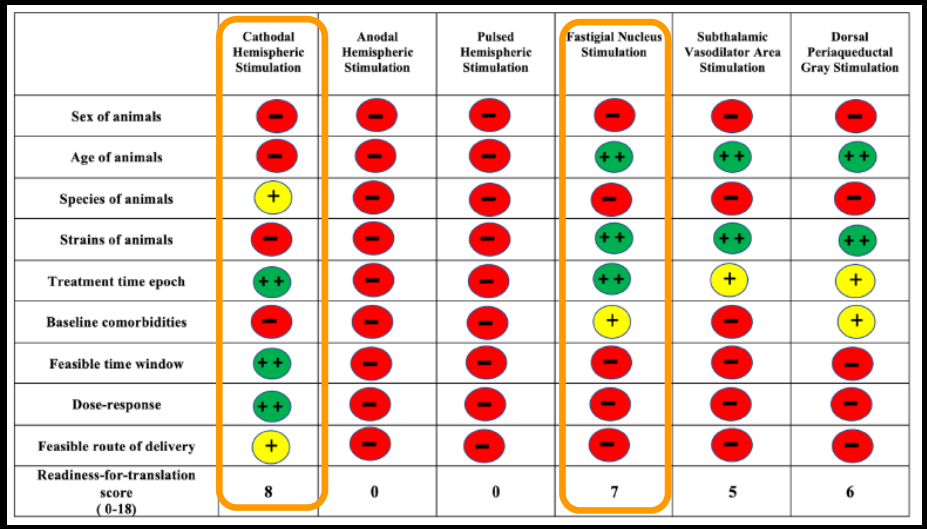



*--Bahr-Hosseini et al, Stroke 2019*

# CNS Transcranial and Direct Electrical Stimulation for Acute Neuroprotection – Preclinical Meta-Analysis

- Intervention-level Readiness-for-Translation Scale
- Highest scores
  - » Transdural DCS cathodal hemispheric stimulation
  - » DBS fastigial nucleus stimulation



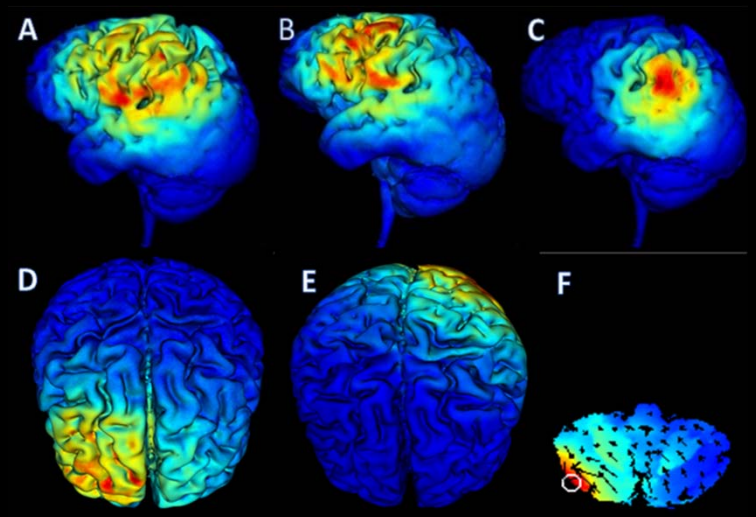
| | Cathodal Hemispheric Stimulation | Anodal Hemispheric Stimulation | Pulsed Hemispheric Stimulation | Fastigial Nucleus Stimulation | Subthalamic Vasodilator Area Stimulation | Dorsal Periaqueductal Gray Stimulation |
|---|---|---|---|---|---|---|
| Sex of animals | − | − | − | − | − | − |
| Age of animals | − | − | − | ++ | ++ | ++ |
| Species of animals | + | − | − | − | − | − |
| Strains of animals | − | − | − | ++ | ++ | ++ |
| Treatment time epoch | ++ | − | − | ++ | + | + |
| Baseline comorbidities | − | − | − | + | − | + |
| Feasible time window | ++ | − | − | − | − | − |
| Dose-response | ++ | − | − | − | − | − |
| Feasible route of delivery | + | − | − | − | − | − |
| Readiness-for-translation score (0-18) | 8 | 0 | 0 | 7 | 5 | 6 |



*--Bahr-Hosseini et al, Stroke 2019*

# Transcranial Electrical Stimulation in Stroke EaRly After onset Clinical Trial (TESSERACT)

- AIS within 24h
  - » Penumbral pattern
  - » Ineligible for IVT
- Dose escalation
  - » 6 tiers
    - 1mA, 2 mA
    - 20 min cycles – 1,2,3
  - » Traditional 3+3 design
  - » 3:1 randomization to active versus sham
- Safety (SICH), feasibility, tolerability, prelim efficacy




*Computational modeling of electrical fields covering: A) M1 MCA; B) M2 superior branch MCA; C) M2 inferior branch MCA; D) ACA; E) PCA; F) PICA*

*UCLA Stroke Center*

*-Bahr Hosseini, Bikson, Unal, Iacoboni, Avila, Liebeskind, Saver, ISC 2020*

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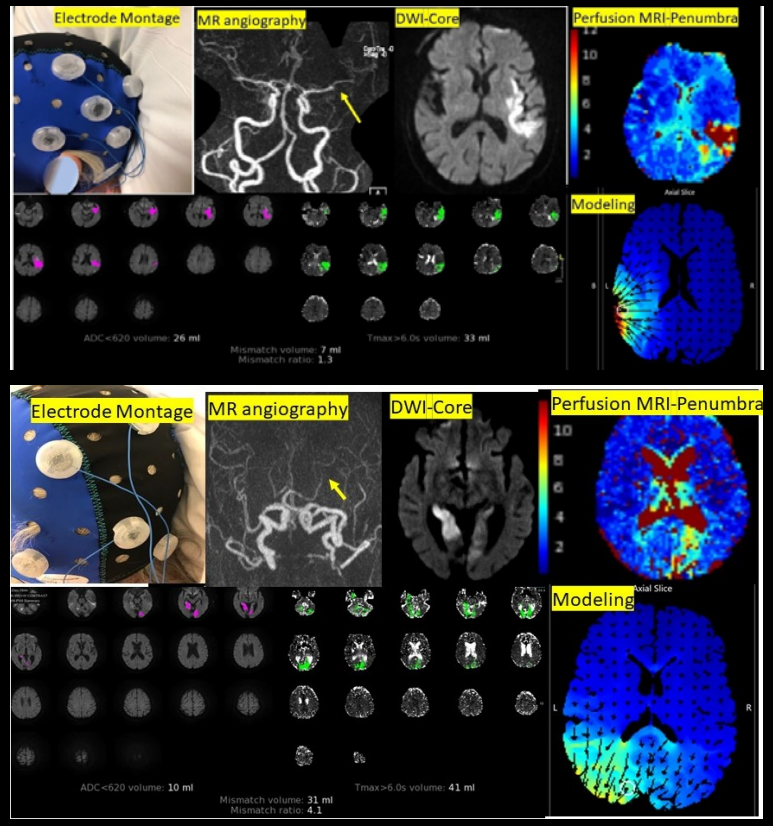


*UCLA Stroke Center*

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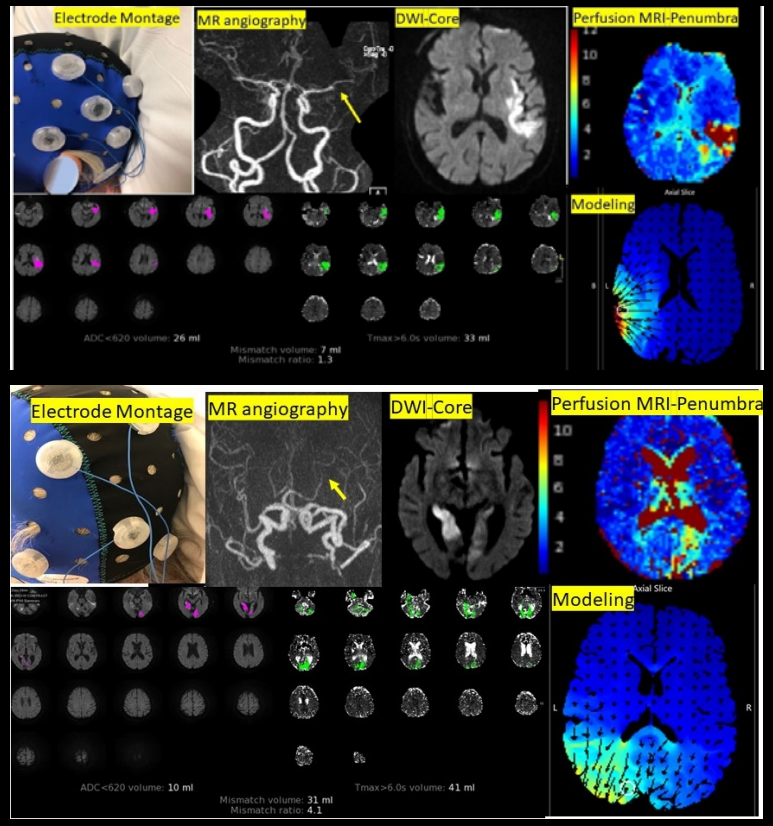


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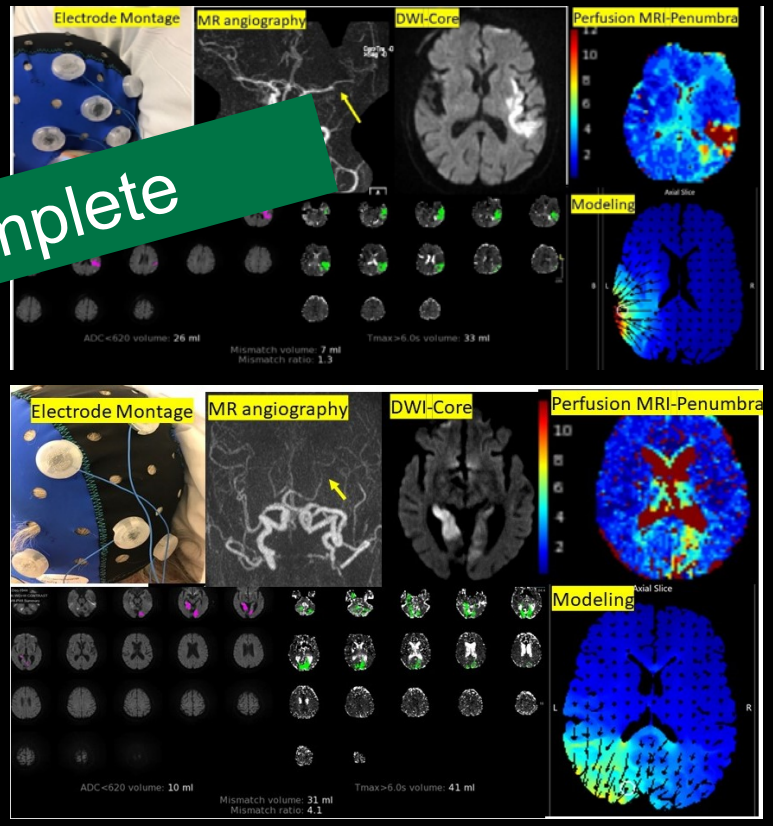
Tier 1 Complete




*UCLA Stroke Center*

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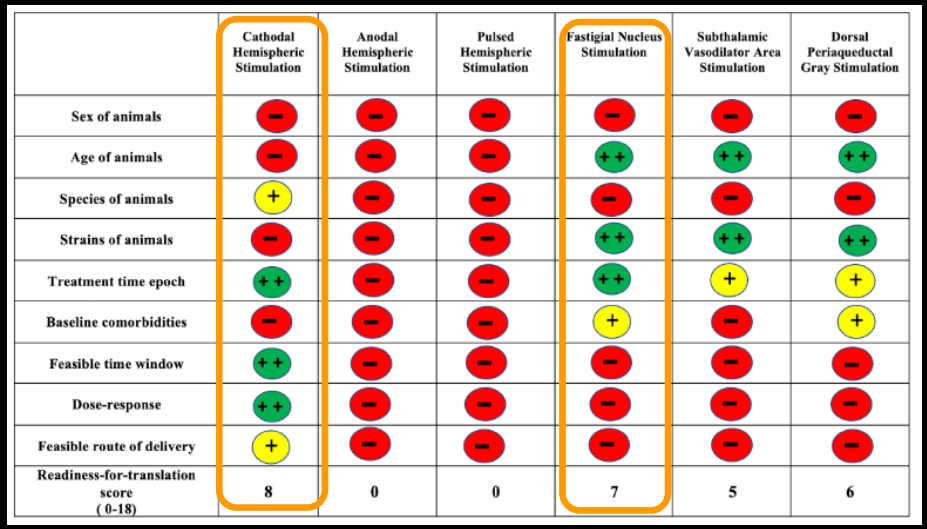
# CNS Transcranial and Direct Electrical Stimulation for Acute Neuroprotection – Preclinical Meta-Analysis

- Intervention-level Readiness-for-Translation Scale
- Highest scores
  - » Transdural cathodal hemispheric stimulation
  - » DBS fastigial nucleus stimulation



| | Cathodal Hemispheric Stimulation | Anodal Hemispheric Stimulation | Pulsed Hemispheric Stimulation | Fastigial Nucleus Stimulation | Subthalamic Vasodilator Area Stimulation | Dorsal Periaqueductal Gray Stimulation |
|---|---|---|---|---|---|---|
| Sex of animals | − | − | − | − | − | − |
| Age of animals | − | − | − | ++ | ++ | ++ |
| Species of animals | + | − | − | − | − | − |
| Strains of animals | − | − | − | ++ | ++ | ++ |
| Treatment time epoch | ++ | − | − | ++ | + | + |
| Baseline comorbidities | − | − | − | + | − | + |
| Feasible time window | ++ | − | − | − | − | − |
| Dose-response | ++ | − | − | − | − | − |
| Feasible route of delivery | + | − | − | − | − | − |
| Readiness-for-translation score (0-18) | 8 | 0 | 0 | 7 | 5 | 6 |



*--Bahr-Hosseini et al, Stroke 2019*

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|---|---|---|---|---|---|---|
| Sex of animals | − | − | − | − | − | − |
| Age of animals | − | − | − | ++ | ++ | ++ |
| Species of animals | + | − | − | − | − | − |
| Strains of animals | − | − | − | ++ | ++ | ++ |
| Treatment time epoch | ++ | − | − | ++ | + | + |
| Baseline comorbidities | − | − | − | + | − | + |
| Feasible time window | ++ | − | − | − | − | − |
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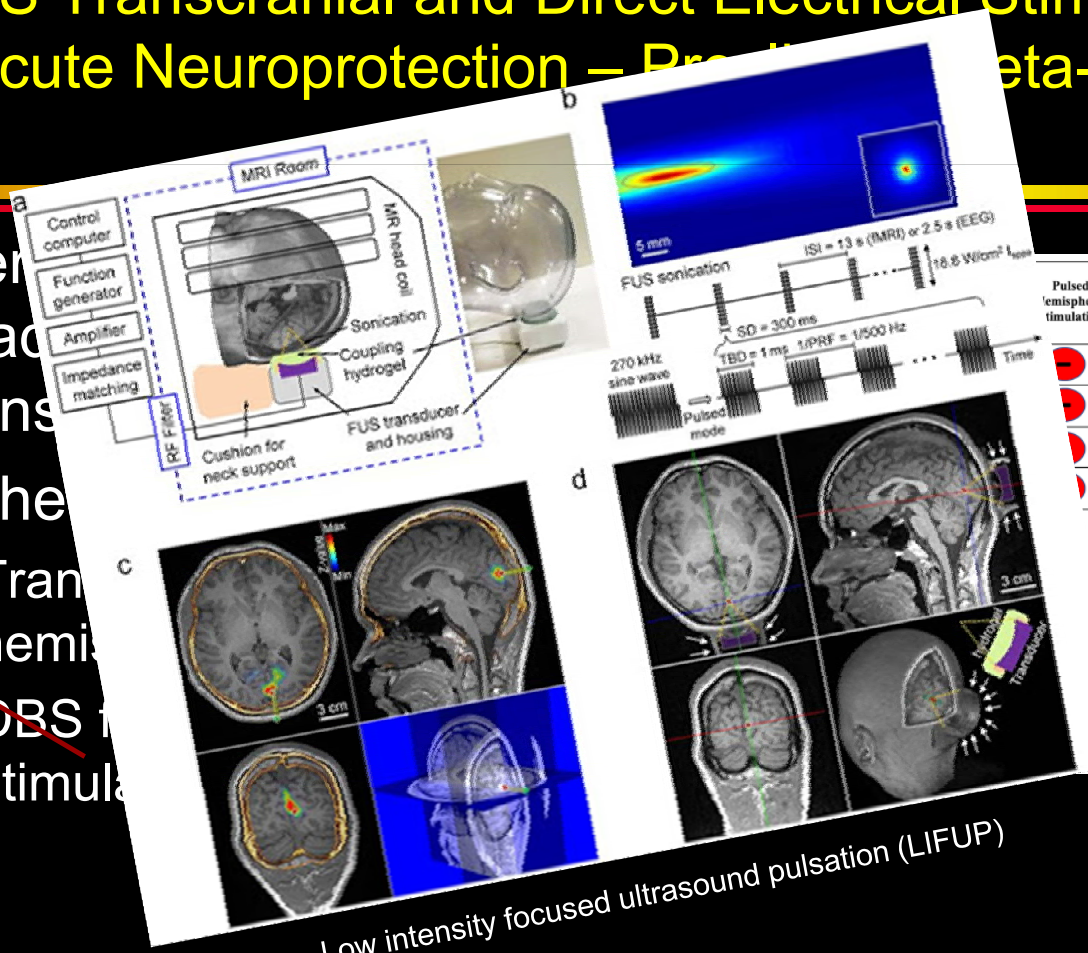
*--Bahr-Hosseini et al, Stroke 2019*

# CNS Transcranial and Direct Electrical Stimulation for Acute Neuroprotection – Pr… eta-Analysis

- Inter… Read… Trans…
- Highe…
  - » Tran… hemi…
  - » DBS … stimul…

FUS




| Pulsed Hemispheric Stimulation | Fastigial Nucleus Stimulation | Subthalamic Vasodilator Area Stimulation | Dorsal Periaqueductal Gray Stimulation |
|---|---|---|---|
| − | − | − | − |
| − | ++ | ++ | ++ |
| − | − | − | − |
| − | ++ | ++ | ++ |
| ++ | ++ | + | + |
| + | + | − | + |
| − | − | − | − |
| − | − | − | − |
| − | − | − | − |
| 6 | 7 | 5 | 6 |

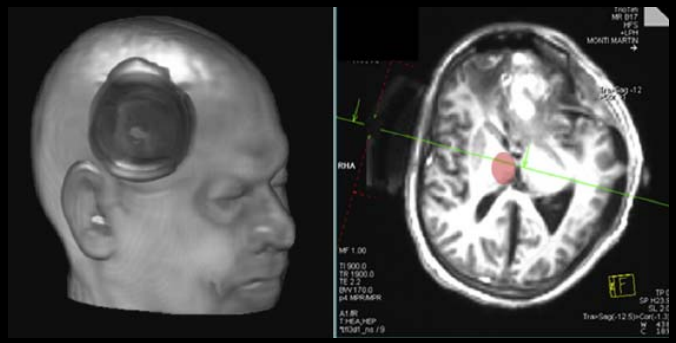
Low intensity focused ultrasound pulsation (LIFUP)

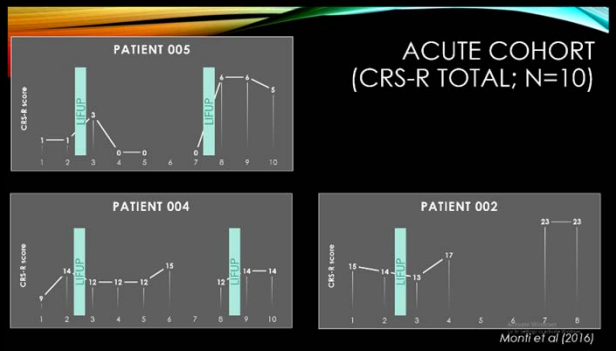


*--Bahr-Hosseini et al, Stroke 2019*

# Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury

- Thalamic LIFUP with pulse rep frequency 100 Hz, pulse width 0.5 ms, 10 sonications, each lasting 30 s
- Improved language comprehension, walking initiation

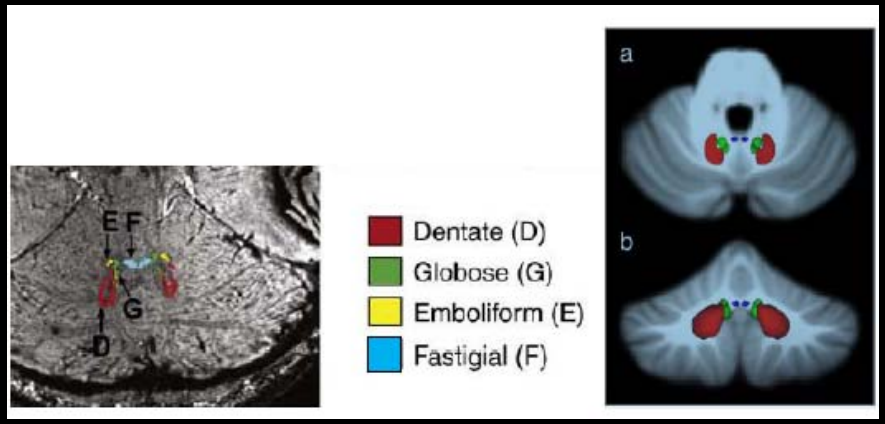





*-Monti, Schnakers, Vespa, Brain Stim 2016*

# Fastigial Nucleus Ultrasound Stimulation Development Program

- FNS Stim Preclinical
  - » During stimulation
    - Increased BP and CBF
      - » "Fastigial pressor response"
      - » Symp and parasymp NS
  - » After stimulation, long-lasting conditioned central neuroprotection
    - Anti-excitotoxic injury
    - Anti-inflammatory
    - Anti-apoptotic
    - Mediated by activation of central cholinergic system
- Normal volunteers
  - » Demonstrate feasibility
- Patients dose escalation
- Patients pivotal



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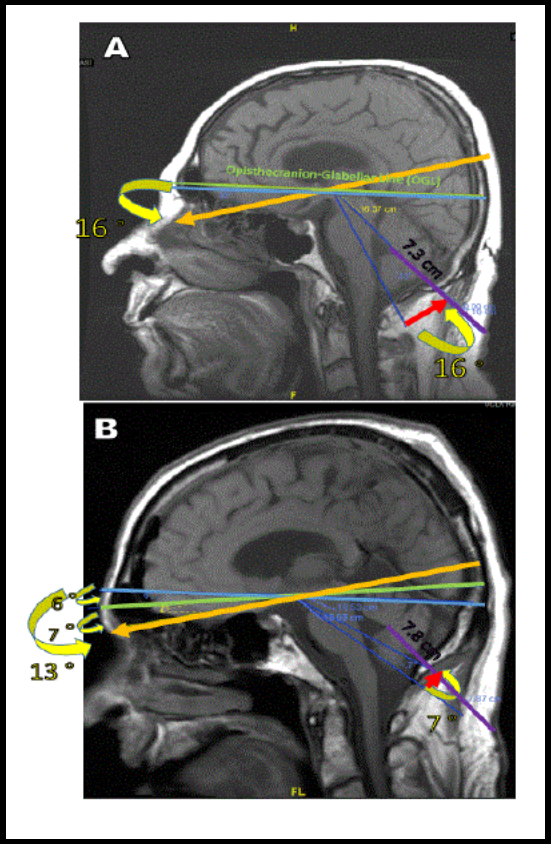
- Patients dose escalation
- Patients pivotal

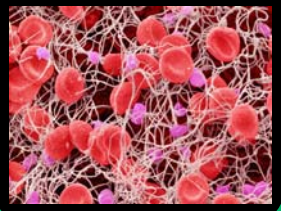



*--Bahr-Hosseini et al, ISC 2020*

# Five Major Strategies to Treat Acute Ischemic Stroke

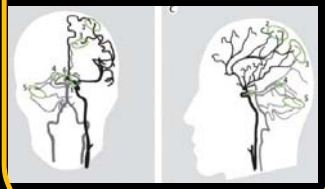
**Supportive Care**

**Avert Clot Propagation**

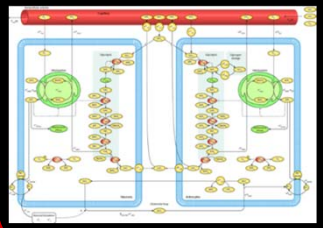


**Recanalization**


**Collateral Enhancement**



**Neuroprotection**



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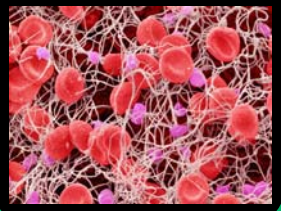

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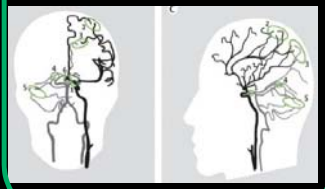

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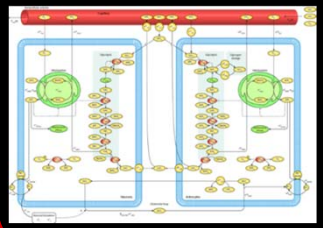


# Three Major Methodologies to Treat Acute Ischemic Stroke

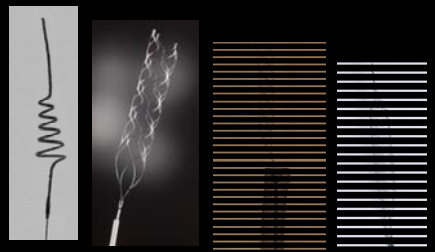
## Pharmacologic


Antiplatelet
1956 (LA)

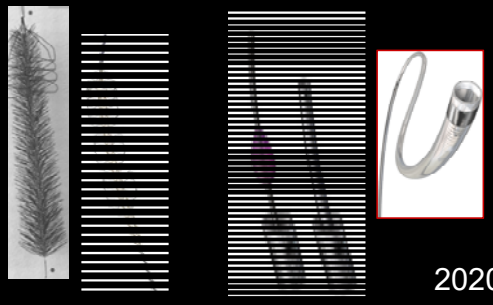

Thrombolytic
1995

Neuroprotective
?? (NA-1)

## Mechanical Endovascular



Coil Retriever
2004 (LA)



2020

## Neuromodulation

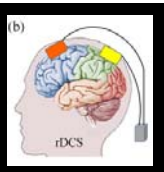
*Peripheral – Electrical + Magnetic*

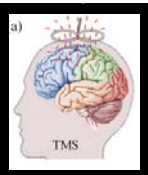
SPG Stim

Vagal N Stim

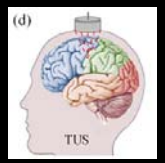
NME Stim

*Central - Electrical + Magnetic*




*Central - Ultrasound*




*UCLA Stroke Center*

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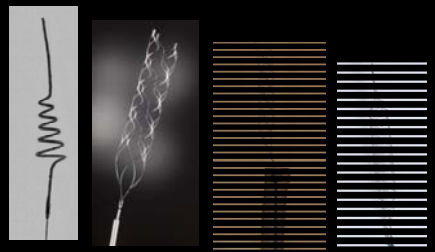

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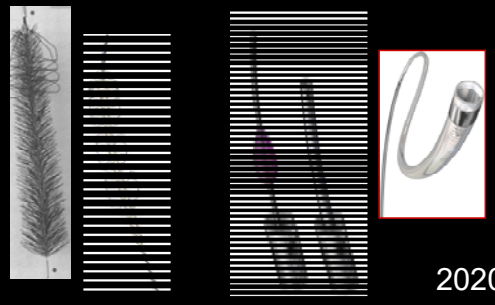

2020

## Neuromodulation

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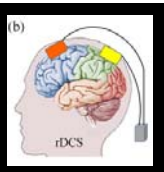
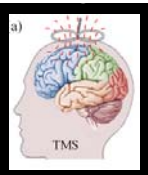
Vagal N Stim

NME Stim

*Central - Electrical + Magnetic*

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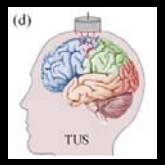


*UCLA Stroke Center*


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