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Stimulation (neuromodulation) for post stroke recovery – ready?

Jesse Dawson

Mechanisms of upper limb impairment / recovery

Neurogenesis?

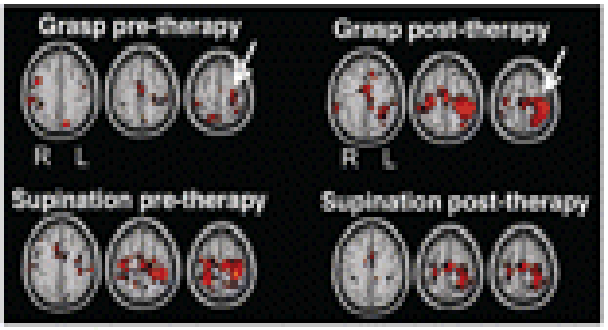
Plasticity?

Inflammation / neuroinhibitory factors?

How does recovery occur?? PLASTICITY

- Plasticity - intrinsic ability of the brain to reorganize its function and structure in response to stimuli and injuries

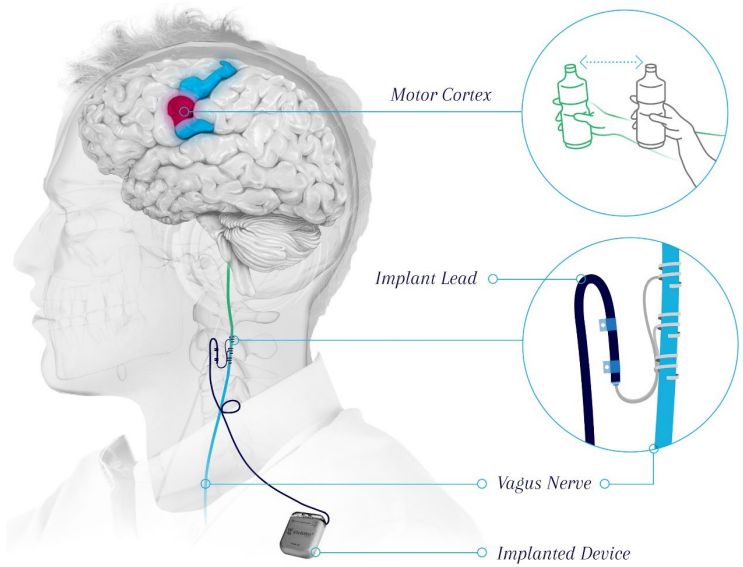
- Changed neural activity and connectivity in perilesional, remote and contralateral legions after stroke
  - Increased ipsilesional activity
  - Inhibitory contralateral effects



Brain, Volume 134, Issue 6, June 2011, Pages 1591–1609, https://doi.org/10.1093/brain/awr039

What do we mean by neuromodulation?

- The alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body



https://www.neuromodulation.com/

(dis) Advantages of neuromodulation vs. drugs

Neuromodulation	Drugs
Expensive / up front capital cost	Cheap
Highly targeted	Off target effects
Highly reversible	Longer action
Continuous / specifically timed	Fixed regimens
Ease of dose optimization	
Potential for closed loop systems	
Invasive	Non-invasive
More effective in some cases	Risk of tolerance

Ting et al. Front. Neurosci2021
https://doi.org/10.3389/fnins.2021.649459

Methods of stimulation

Repetitive

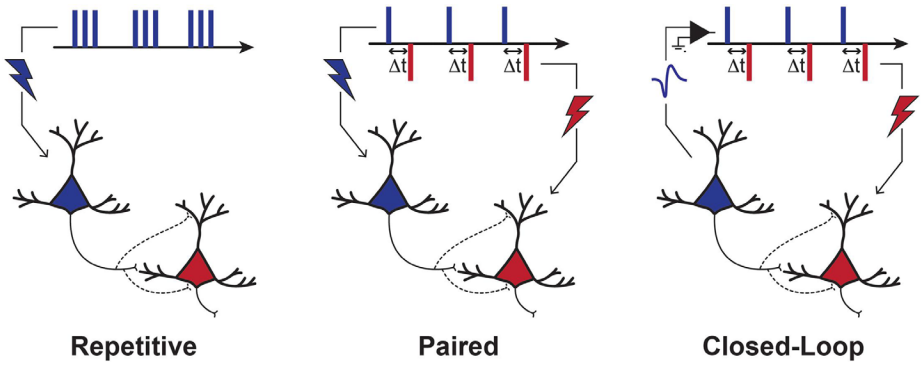
- TMS
- tDCS
- Invasive electrical stimulation

Paired stimulation

- TMS + peripheral stimulation

Closed loop stimulation

- Behaviour controlled
- EEG controlled



Ting et al. Front. Neurosci2021
https://doi.org/10.3389/fnins.2021.649459

Main areas of progress

Improvement of motor impairment

- VNS
- TMS
- tDCS
- Direct epidural stimulation

Treatment of spasticity

- NMES

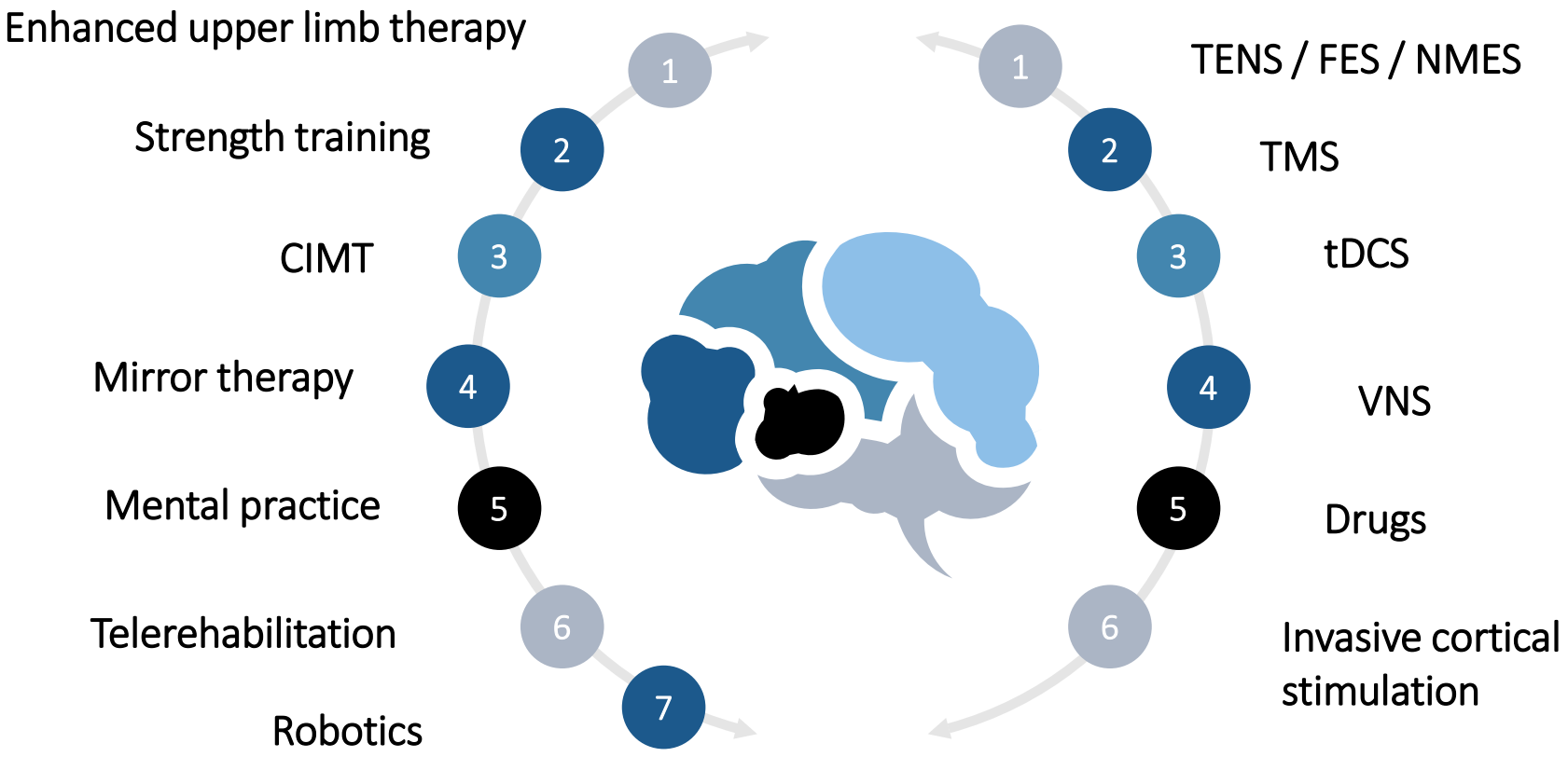
Treatment of dysphagia

- Pharyngeal stimulation

Augmentation of collateral blood flow

- SPGS

What are the options for impairment?



Promote plasticity - learning

Change propemsity for plasticity

Do these treatments work?

	Impairment	Function	Spasticity	ADLs	Global function
Enhanced therapy	↑↑↑	↑	↑		☒
Robotics	↑↑↑				☒
Strength	↑				☒
VR	↑				☒
CIMT	↑↑↑	↑↑	↑	↑↑	☒
Mirror therapy	↑				☒
FES / NMES	↑		↑		☒
TMS	↑↑	↑↑		↑	☒
VNS	↑↑↑	↑			?
tDCS	↑		↑		☒
Botulinum toxin			↑↑↑		

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Paired VNS based rehabilitation

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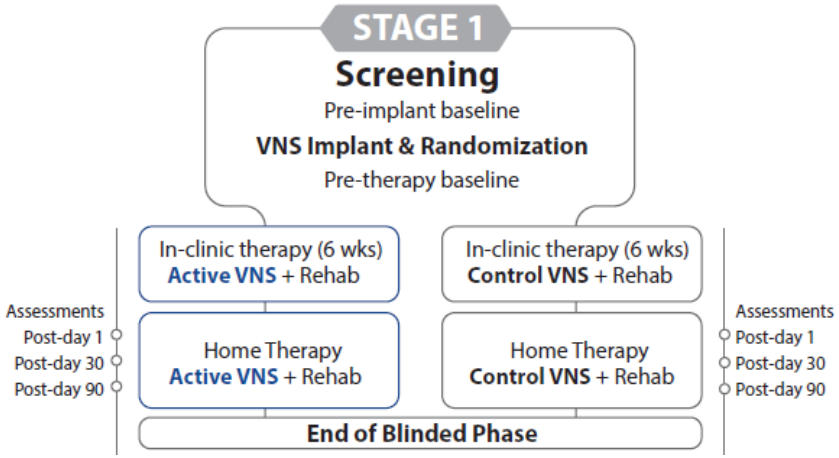
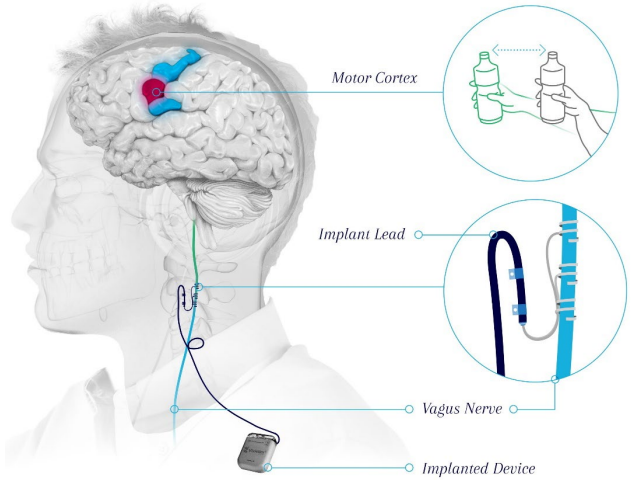
FDA IDE #G170031
UK MHRA No #CI/2015/0011
Clinicaltrials.gov NCT03131960

Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial

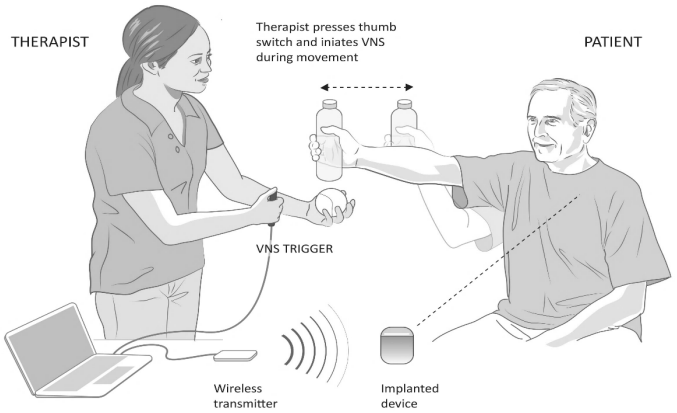
Jesse Dawson, Charles Y Liu, Gerard E Francisco, Steven C Cramer, Steven L Wolf, Anand Dixit, Jen Alexander, Rushna Ali, Benjamin L Brown, Wuwei Feng, Louis DeMark, Leigh R Hochberg, Steven A Kautz, Arshad Majid, Michael W O'Dell, David Pierce, Cecília N Prudente, Jessica Redgrave, Duncan L Turner, Navzer D Engineer, Teresa J Kimberley

Dawson J et al. Lancet. 2021;397:1545-1553

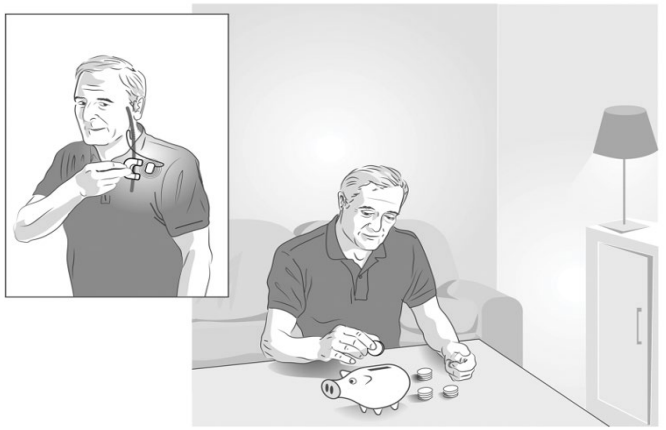




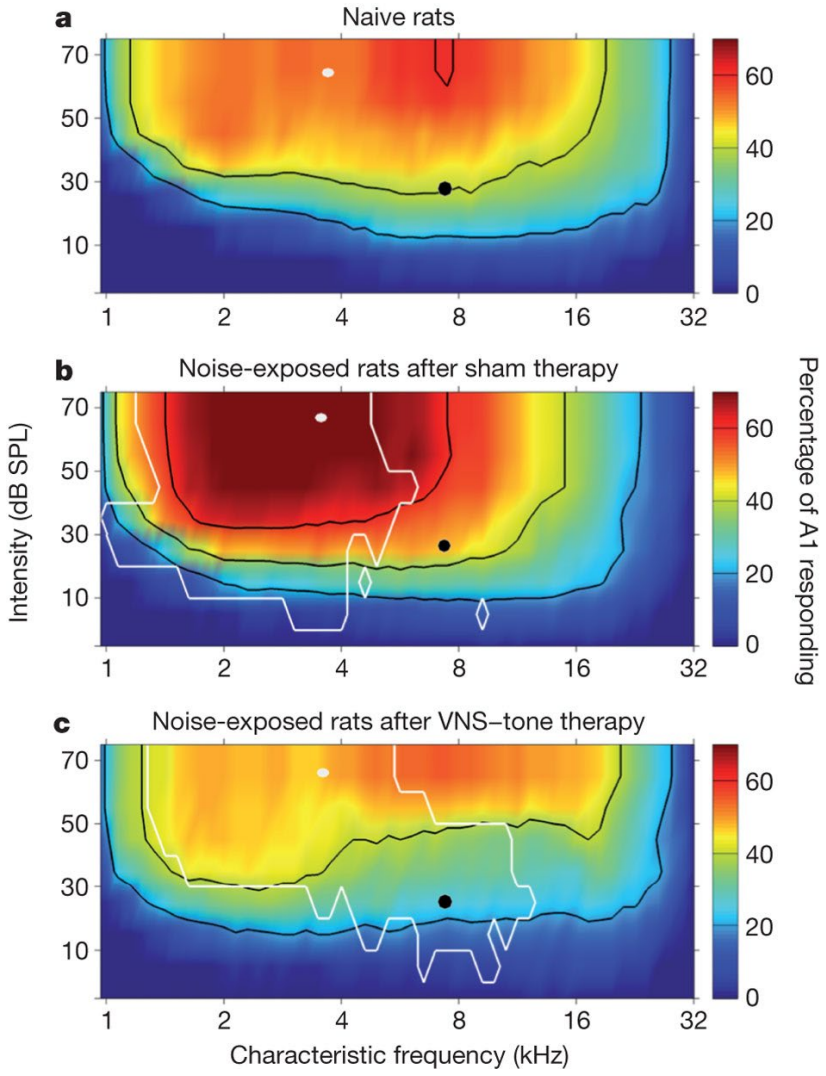
In-clinic Rehabilitation Therapy



Home-based Rehabilitation Therapy



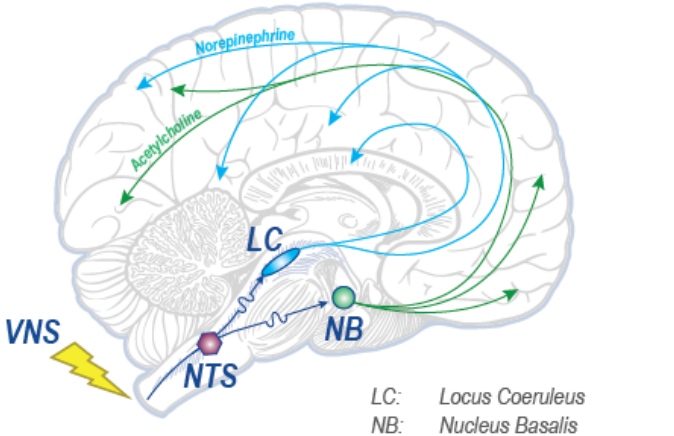
Potential mechanisms of VNS therapy

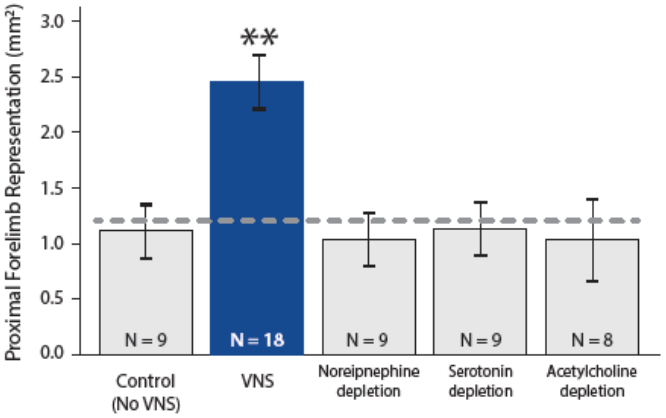


Engineer N et al. Nature. 2010;470:101-104

MECHANISM OF ACTION

VNS activates **release of neuromodulators** which facilitate behavioral and physiological change





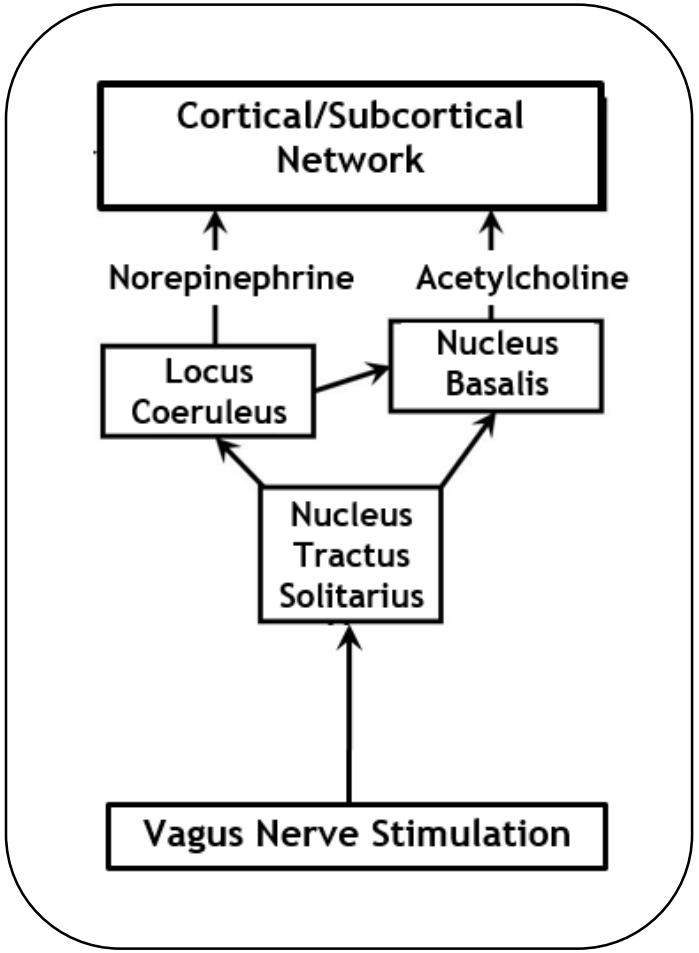
Hulsey et al., 2017

VNS paired with intense rehabilitation

Intense Rehabilitation

+

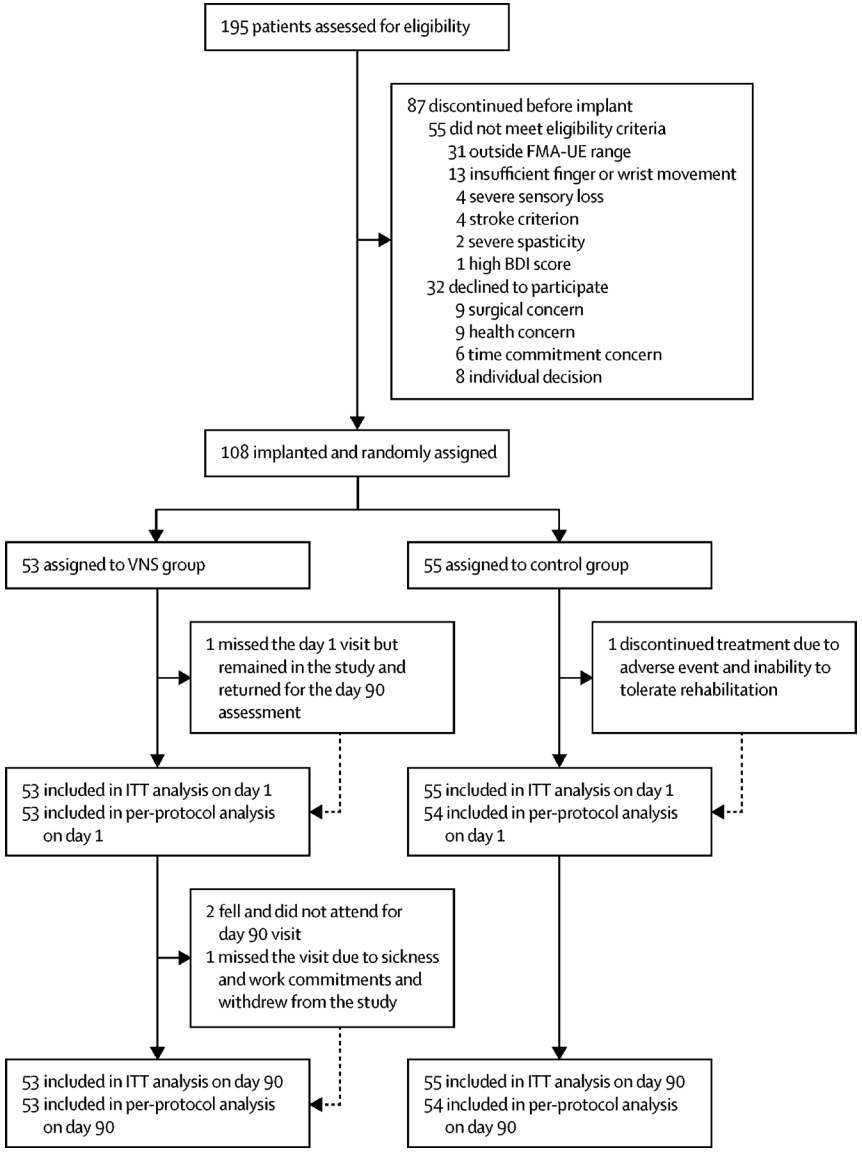
Neuromodulator Release



= Increased Plasticity

Trial profile

107 participants completed intervention, 106 attended for primary outcome



	VNS group (n=53)	Control group (n=55)
Age, years	59·1 (10·2)	61·1 (9·2)
Sex		
Male	34 (64%)	36 (65%)
Female	19 (36%)	19 (35%)
Race*		
White	42 (79%)	43 (78%)
African American	9 (17%)	9 (16%)
Asian, Indian, or other	1 (2%)	4 (7%)
Not reported	1 (2%)	1 (2%)
Time since stroke, years	3·1 (2·3)	3·3 (2·6)
Handedness		
Right	48 (91%)	50 (91%)
Left	4 (8%)	5 (9%)
Ambidextrous	1 (2%)	0
Side of paresis		
Right	25 (47%)	26 (47%)
Left	28 (53%)	29 (53%)
FMA-UE baseline score	34·4 (8·2)	35·7 (7·8)
WMFT-Functional score	2·71 (0·70)	2·83 (0·65)

Data are n (%) or mean (SD). Some percentages can add up to more than 100% due to rounding. VNS=vagus nerve stimulation. FMA-UE=Fugl-Meyer Assessment-Upper Extremity. WMFT=Wolf Motor Function Test. *Participants could select more than one option for race.

Table: **Baseline demographics and characteristics of the intention-to-treat population**

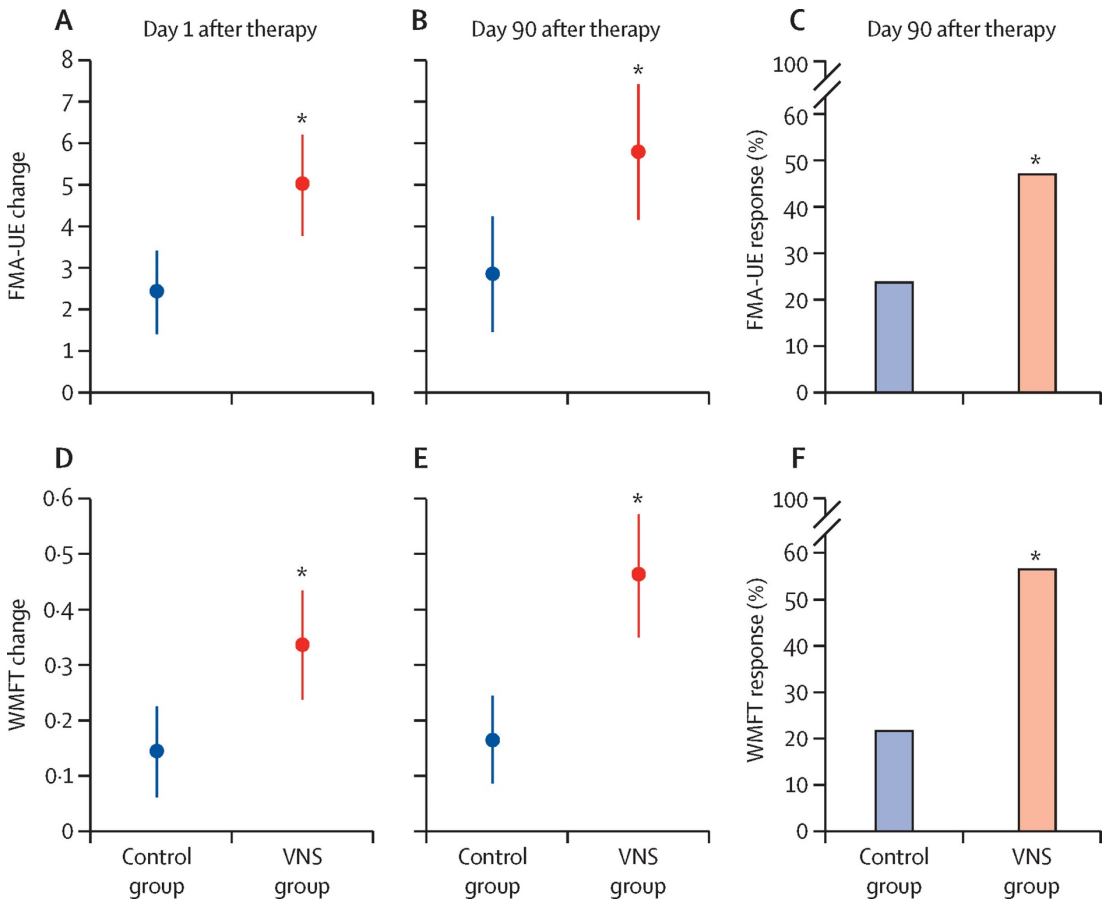
Dawson J et al. Lancet. 2021;397:1545-1553

Safety and adverse events

- 1 VC palsy
- 2 lead replacements required

	Active VNS	Control
Number of serious adverse events	5	3
Number of participants with serious adverse events	5	3
Number of serious adverse device events	0	0
Number of participants with serious adverse device events	0	0
Number of unexpected serious adverse device events	0	0
Number of participants with unexpected serious adverse device events	0	0
Number of NS adverse events	163	171
Number of participants with NS adverse events	43	42
Number of NS adverse device events (possible, probably, definite, total)	12,7,9 (28)	8,4,2 (14)
Number of participants comprising these NS adverse device events	2,4,7 (13)	5,2,2 (9)

VNS Rehab results



- N=108
- Average change in VNS group

Dawson J et al. Lancet. 2021;397:1545-1553

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Was the study blinded?

	Think VNS Group	Think Control Group / Did Not Know	P Value
VNS (n=49)	9 (18%)	40 (82%)	>0.999
Control (n=54)	9 (17%)	45 (83%)	
103 participants completed the questions.			

Key questions re VNS

Is this magnitude of treatment effect important?

- Small between group difference
- Absolute change in VNS group larger
- *"We see differences of 6 points in clinical practice all the time"*

Do we need a 6-point difference between groups?

- Is the response of others relevant to the response of an individual?
- Would we have had a 6-point difference if we had a usual care control?

Is a 6 point change the correct definition of important response?

Are risks and costs worth taking?

Effects in ICH and very severe impairment

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FDA approval in August 2021

FDA NEWS RELEASE

FDA Approves First-of-Its-Kind Stroke Rehabilitation System

Share | Tweet | Linkedin | Email | Print

to treat moderate to severe upper extremity motor deficits associated with chronic ischemic stroke

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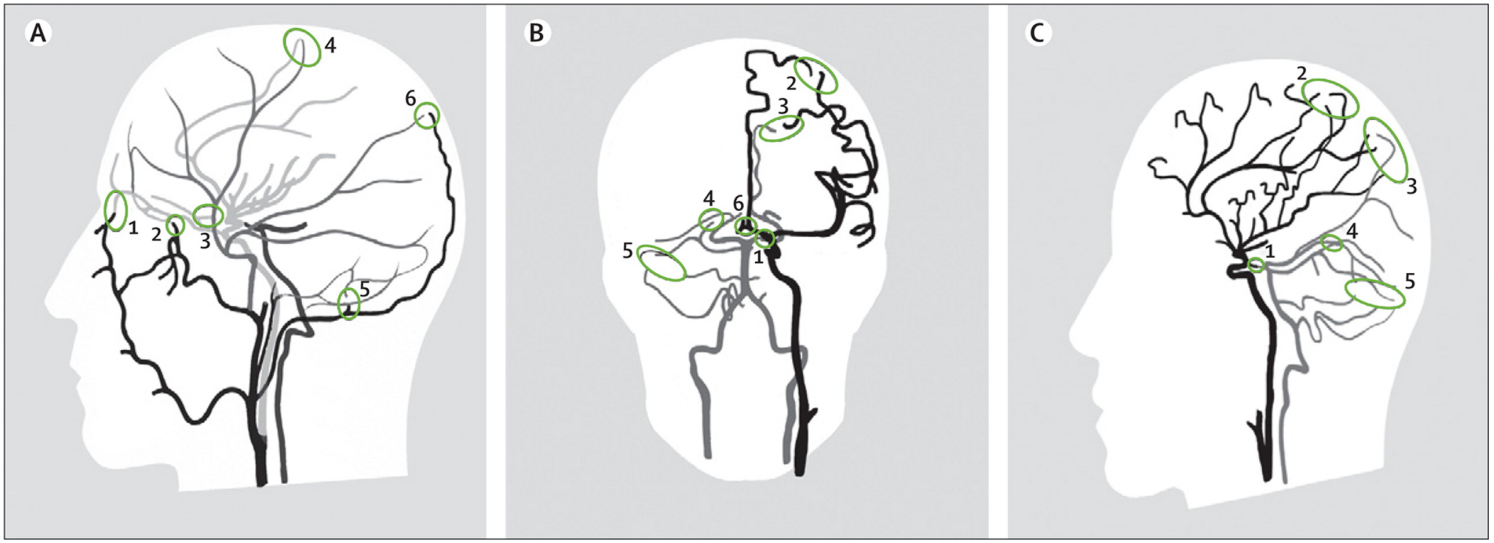
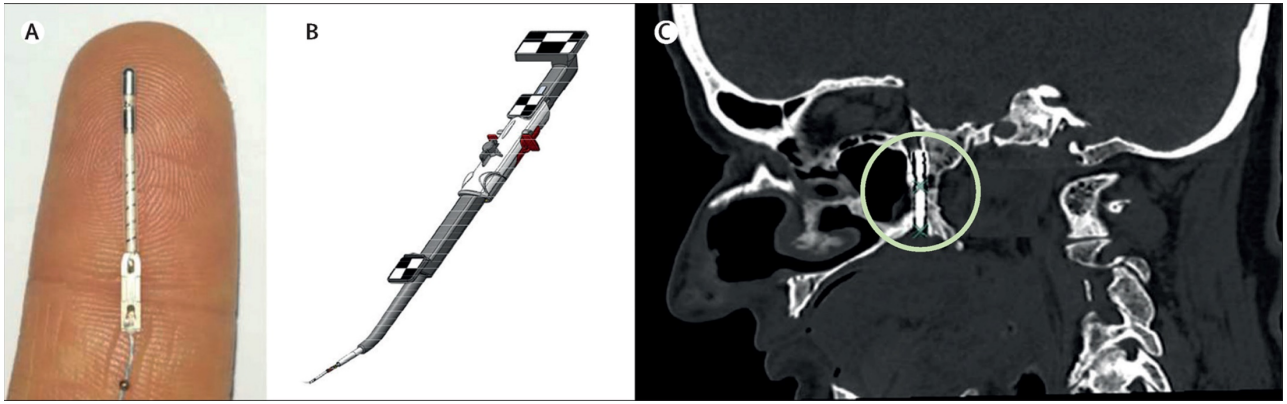
SPGS

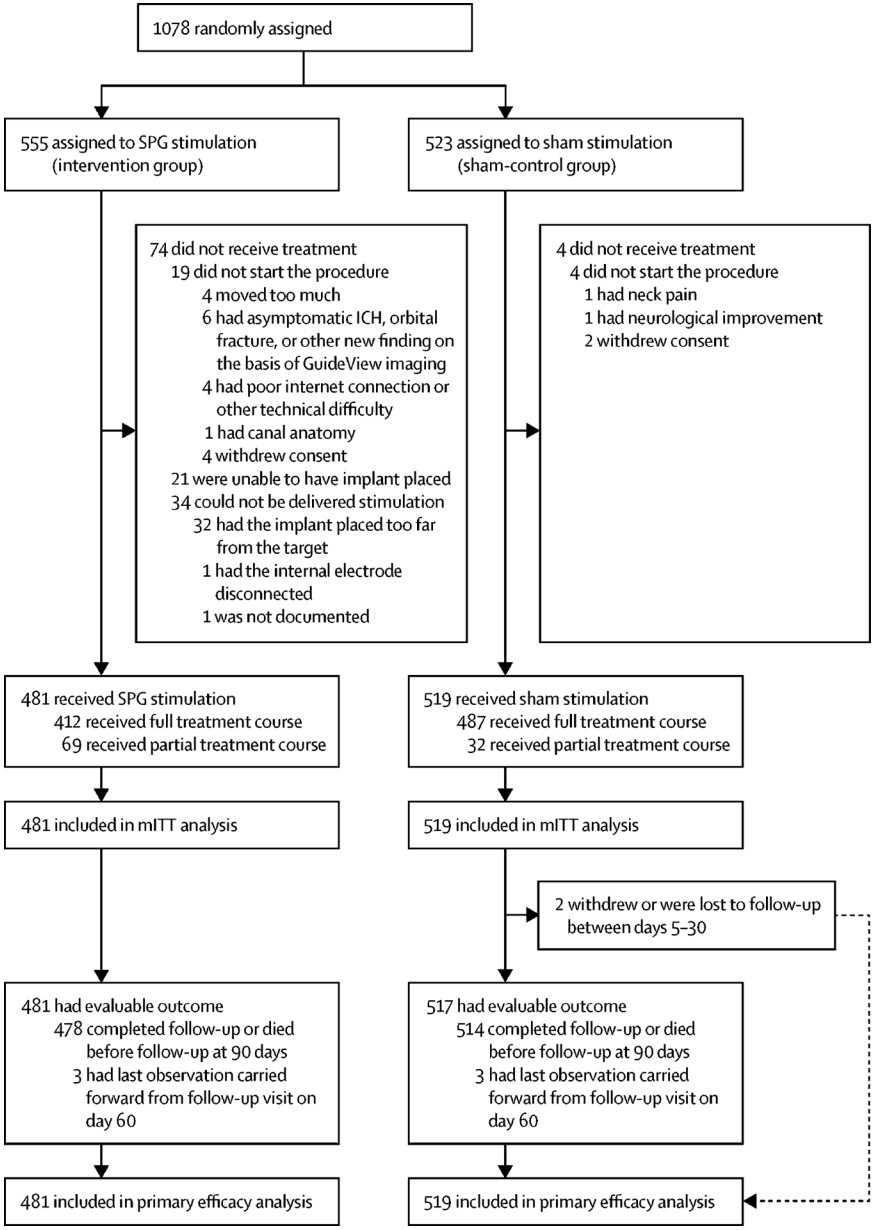
Why SPGS?



Shuaib et al. Lancet Neuro 2011;10:909-921



Bornstein et al. Lancet 2019;394:219-229

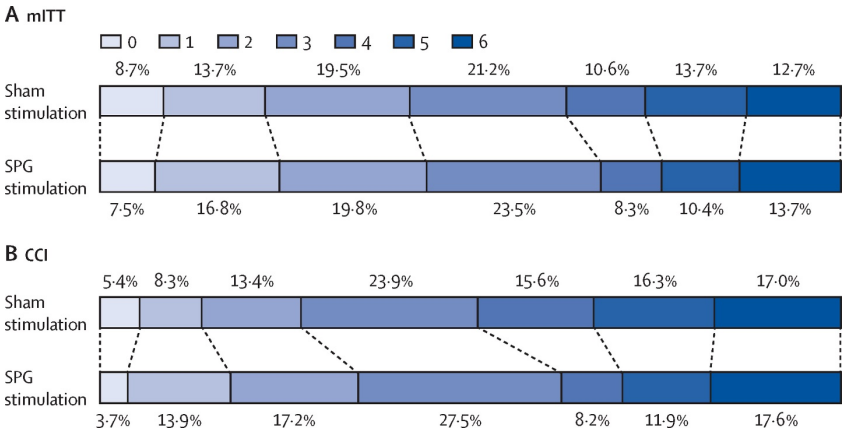


An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial

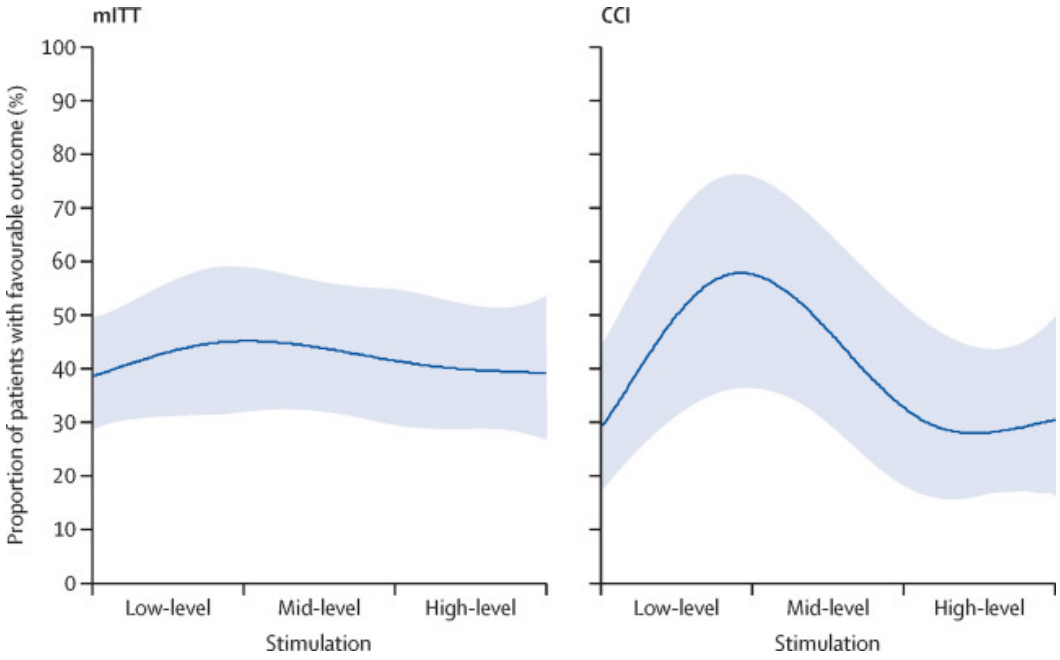
Natan M Bornstein, Jeffrey L Saver*, Hans Christoph Diener, Philip B Gorelick, Ashfaq Shuaib, Yoram Solberg, Lisa Thackeray, Milan Savic, Tamar Janelidze, Natia Zarqua, David Yarnitsky, Carlos A Molina, for the ImpACT-24B investigators*

Bornstein et al. Lancet 2019;394:219-229

ImpACT-24B

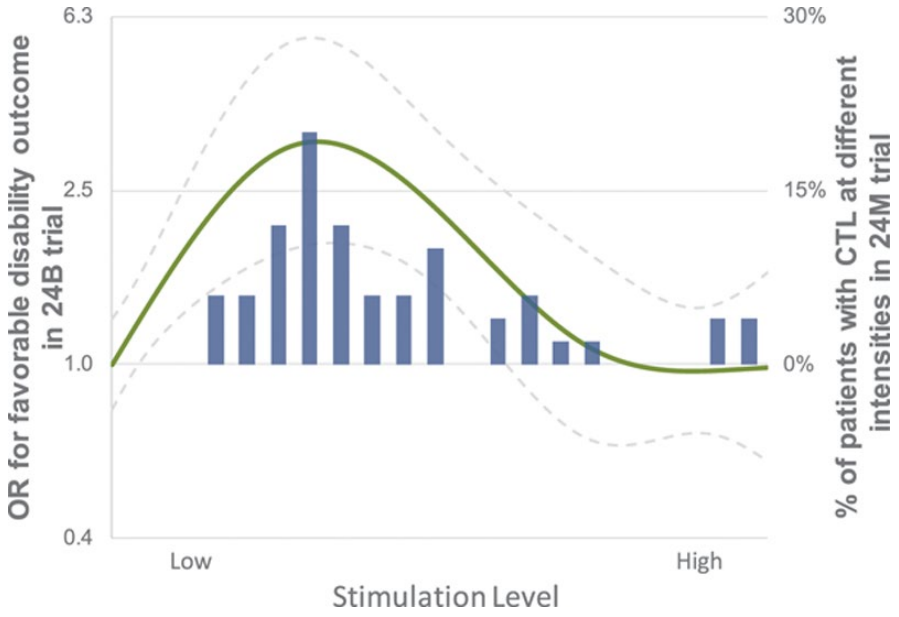


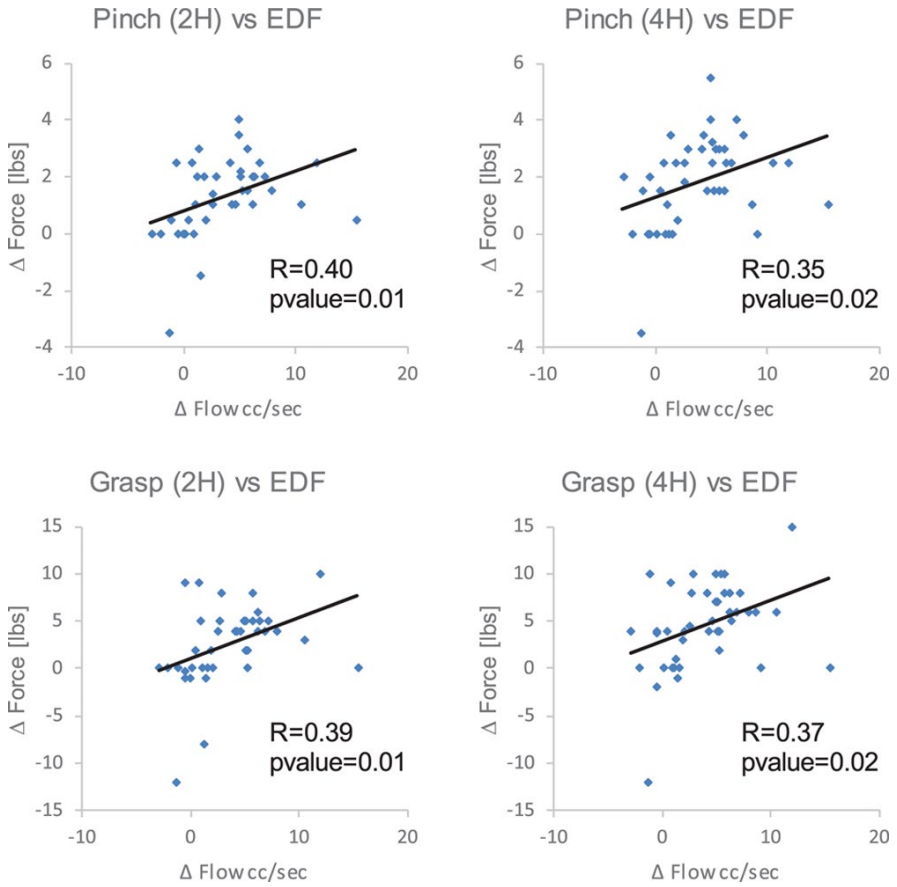
CCI population - improved beyond expectation OR 1·48, 1·05–2·10; p=0·0258



Bornstein et al. Lancet 2019;394:219-229

ImpACT-24M





Saver et al. Stroke 2019;50:3512-18

Summary

- Neuromodulation techniques allow a degree of precision and timing which cannot be achieved by drugs
- This pairing with rehabilitation inputs has been shown to drive task specific plasticity
- Techniques have already begun to show success in well conducted pivotal trials
  - VNS
  - SPGS
  - Pharyngeal stimulation

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