Mass General Brigham

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Optimized Non-Invasive Brain stimulation for Chronic Pain
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Disclosure

Nothing to disclose

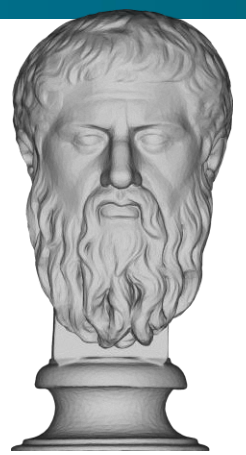
Agenda

1. Introduction
2. Chronic pain
3. Non-invasive brain stimulation techniques
4. Randomized Clinical Trial

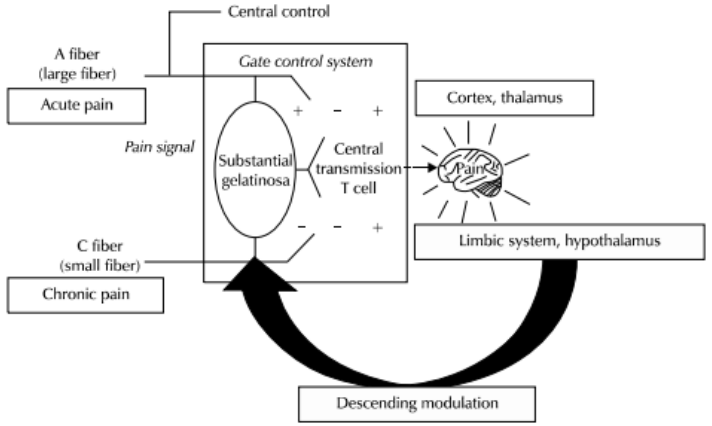
Brief History of Pain

Pain?

- Sensation?
- Symptom?
- Emotion?

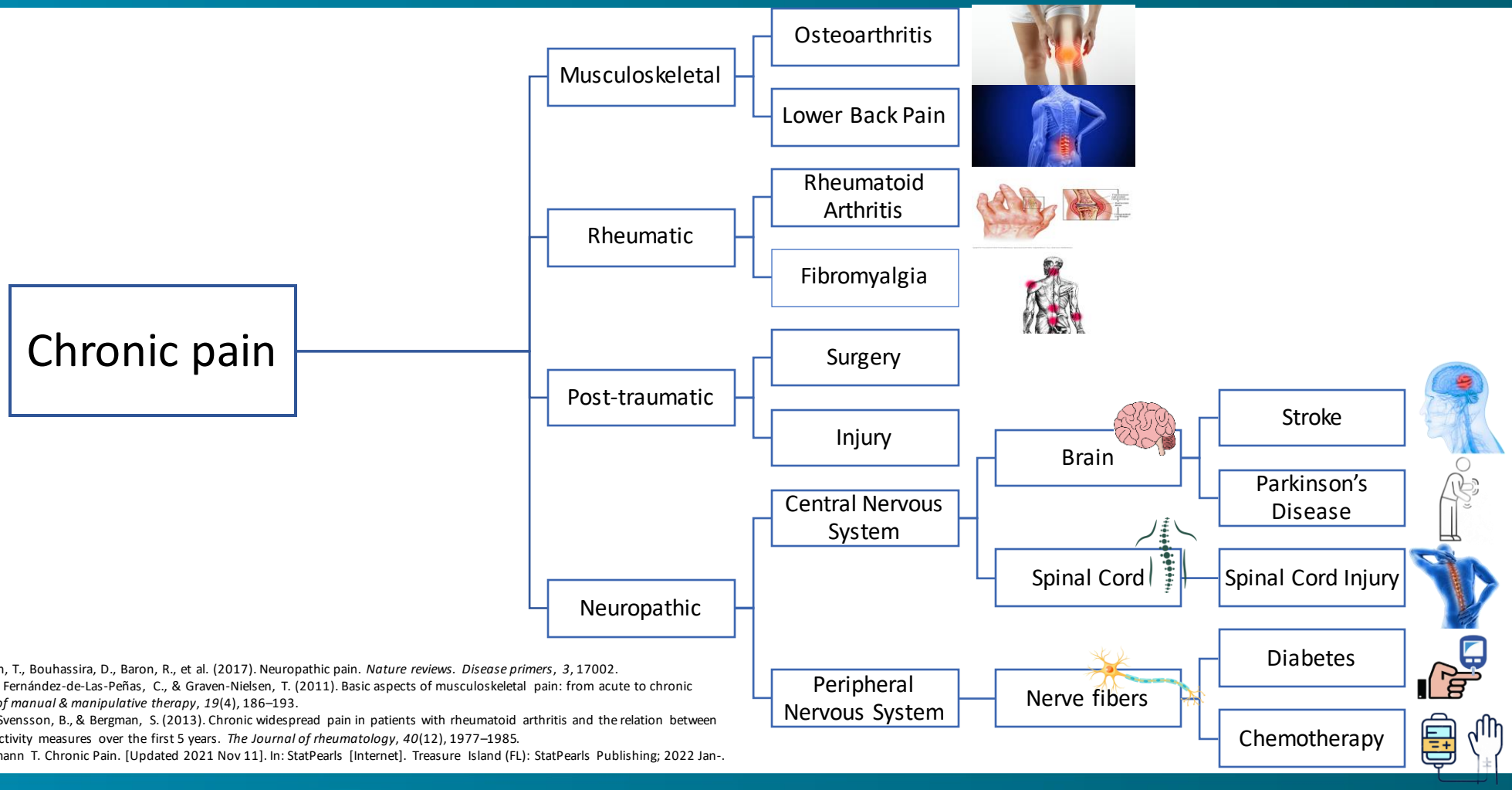


René Descartes
(1596 – 1650)



Murad Ahmad Khan, Fauzia Raza, Iqbal Akhtar Khan. 2015. PAIN: HISTORY, CULTURE AND PHILOSOPHY
In-Chang Cho, Seung Ki Min. Proposed New Pathophysiology of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Chronic pain



Colloca, L., Ludman, T., Bouhassira, D., Baron, R., et al. (2017). Neuropathic pain. *Nature reviews. Disease primers*, *3*, 17002.
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Andersson, M. L., Svensson, B., & Bergman, S. (2013). Chronic widespread pain in patients with rheumatoid arthritis and the relation between pain and disease activity measures over the first 5 years. *The Journal of rheumatology*, *40*(12), 1977–1985.
Dydyk AM, Conermann T. Chronic Pain. [Updated 2021 Nov 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

Pain Pathway in Healthy Subjects

- Neuroimaging have identified brain regions activated by noxious stimuli:

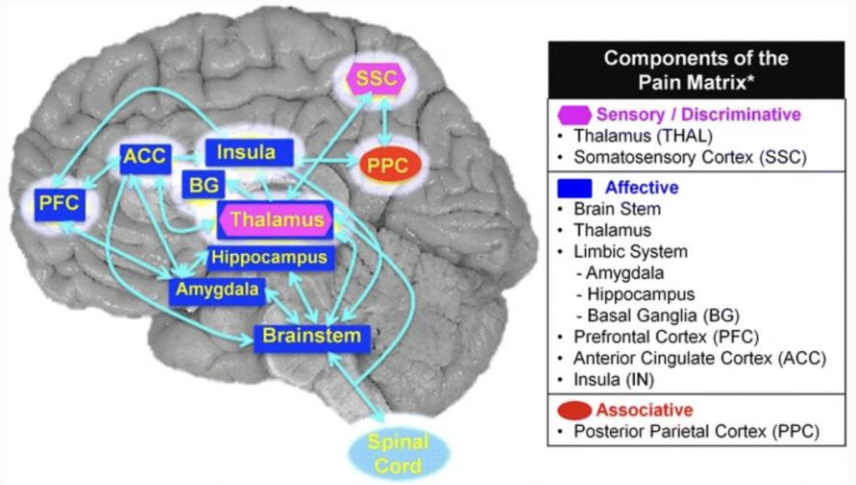
  - Primary somatosensory cortex
  - Secondary somatosensory cortex
  - Insula

  Sensory features

  - Anterior Cingulate cortex (ACC)
  - Prefrontal cortex
  - Amygdala
  - Mesolimbic reward circuit

  Emotional, motivational responses

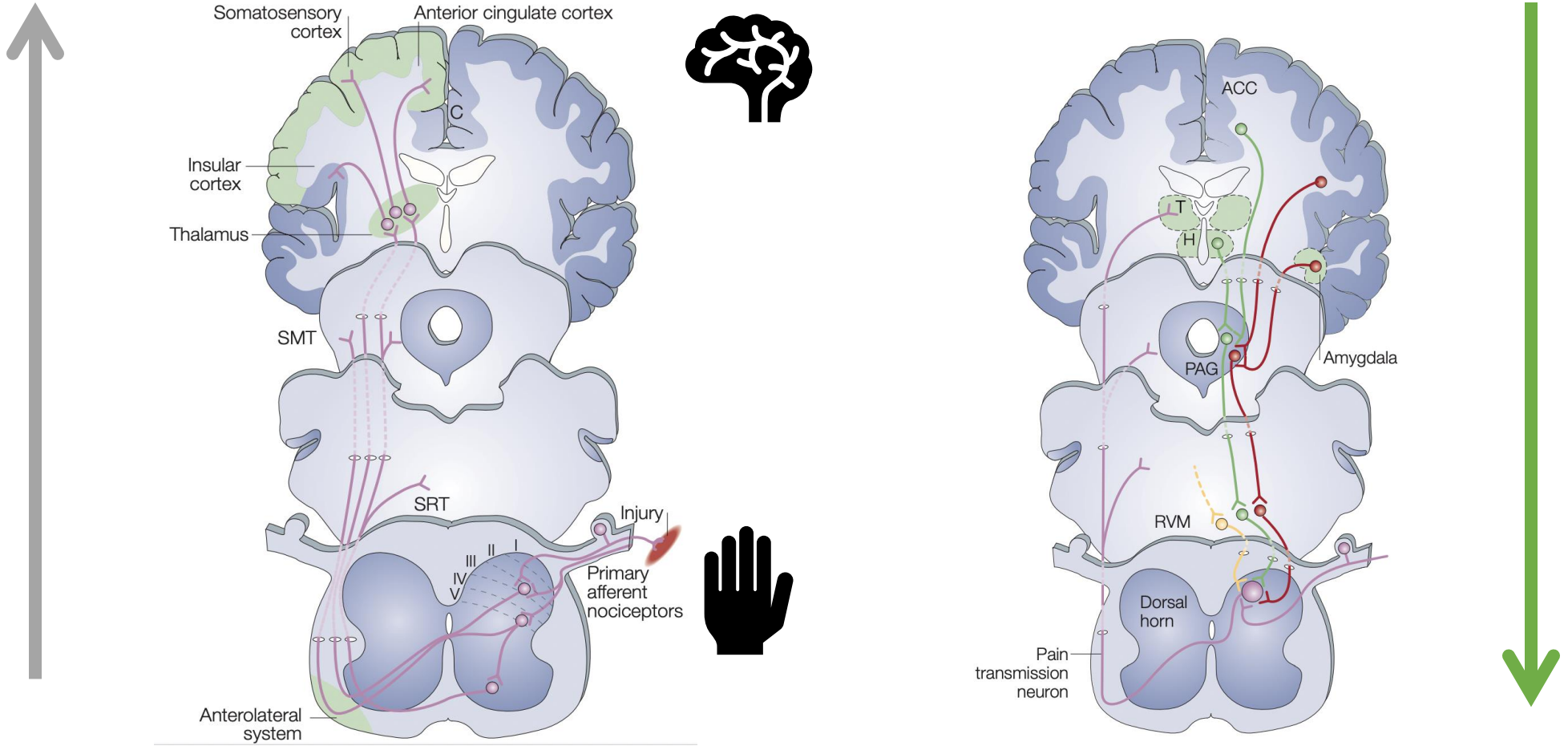
  - Thalamus
  - Cerebellum



Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care. 2014 June;8(2):143-151.

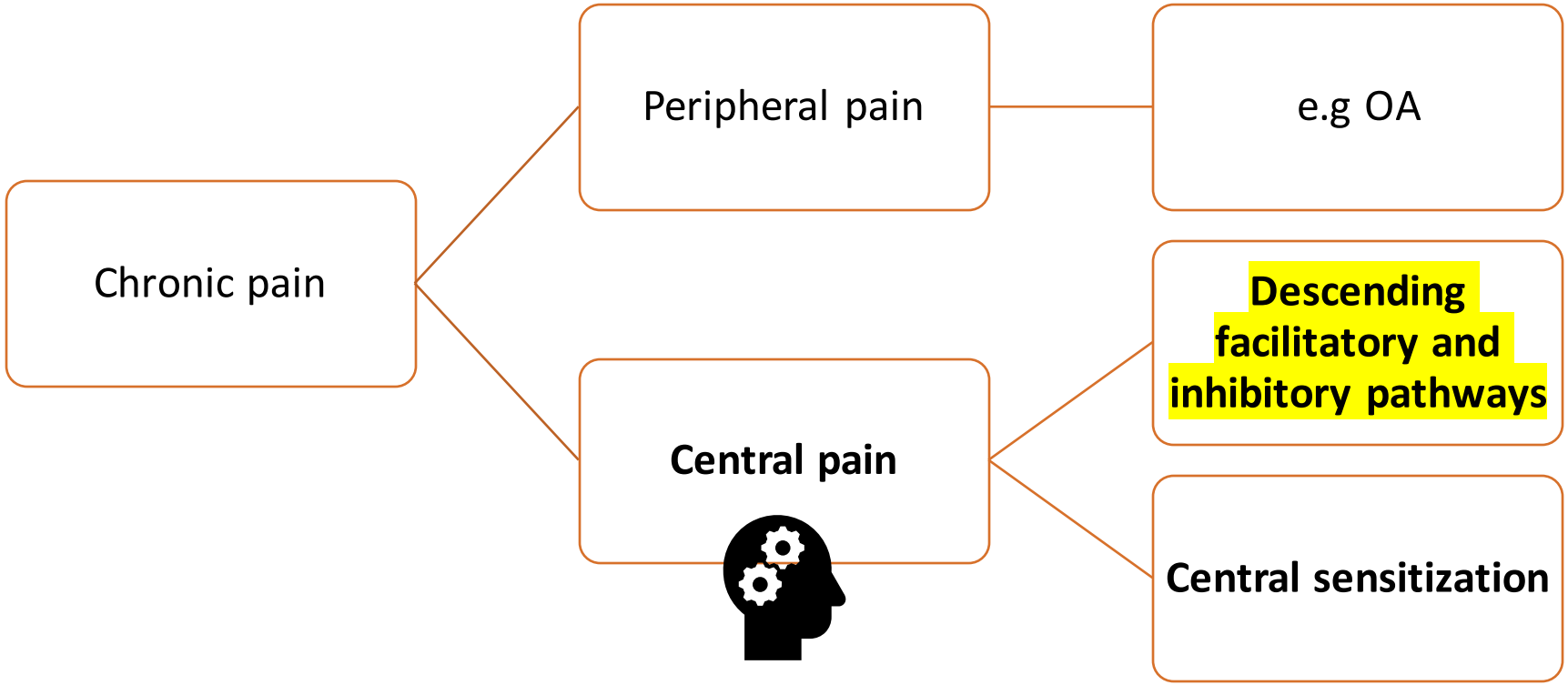
Castillo, D., Ernst, T., Cunningham, E. et al. Altered Associations between Pain Symptoms and Brain Morphometry in the Pain Matrix of HIV-Seropositive Individuals. J Neuroimmune Pharmacol 13, 77–89 (2018)

Endogeneous pain control system



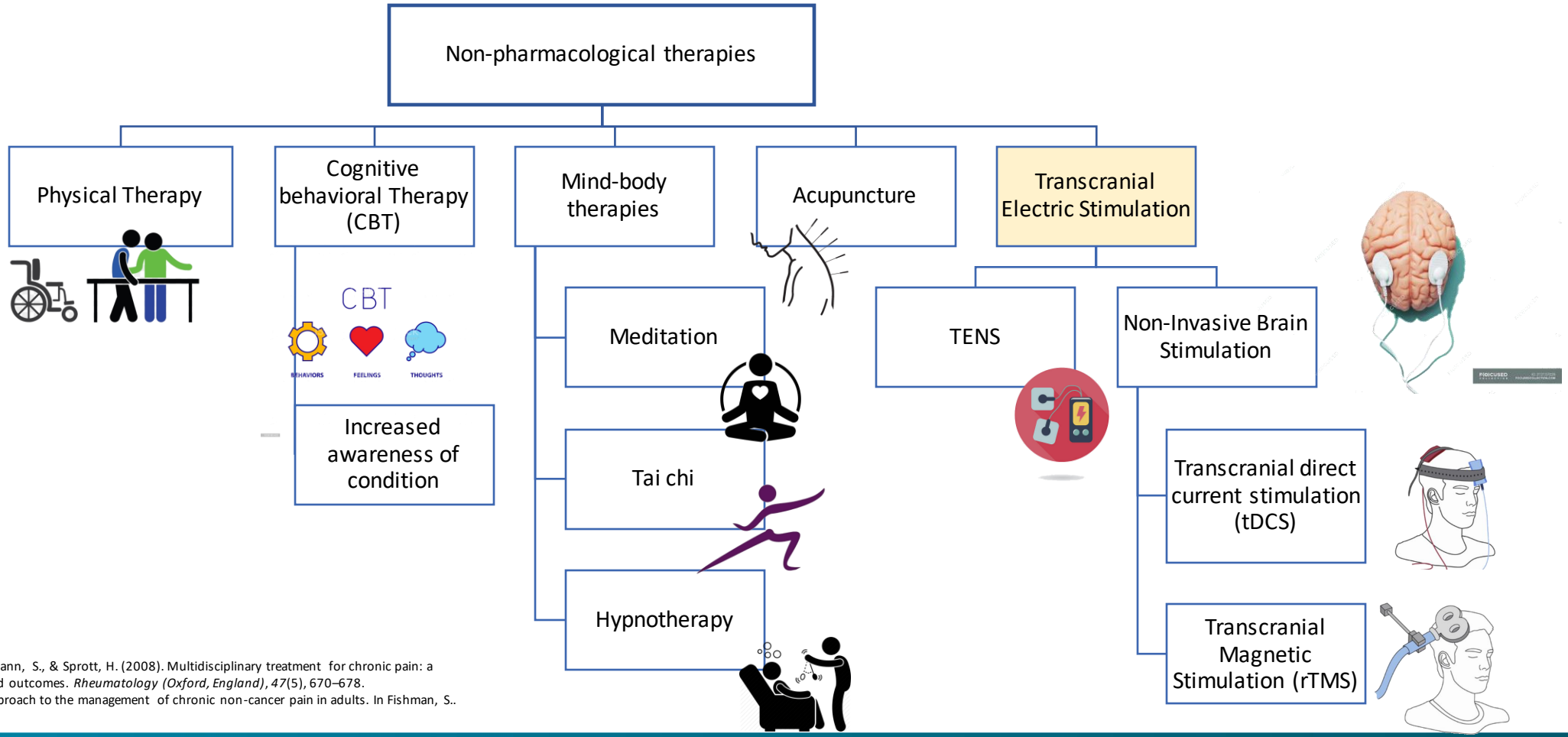
Fields H. State-dependent opioid control of pain. Nat Rev Neurosci. 2004 Jul;5(7):565-75. doi: 10.1038/nrn1431. PMID: 15208698.

Chronic pain



Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther. 2011 Apr 28;13(2):211.

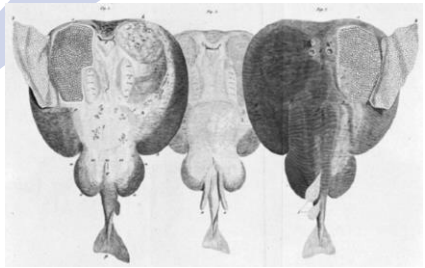
Non-Pharmachological therapies

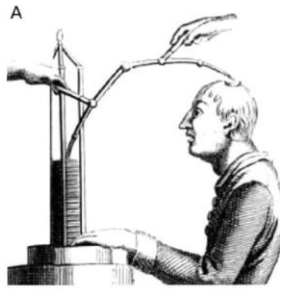


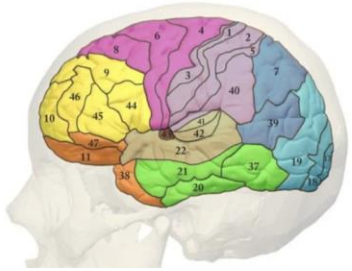
Scascighini, L., Toma, V., Dober-Spielmann, S., & Sprott, H. (2008). Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology (Oxford, England)*, *47*(5), 670–678.
Tauben, D., & Stacey, B. R. (2020). Approach to the management of chronic non-cancer pain in adults. In Fishman, S.. Editor & Crowley, M. *UpToDate*.

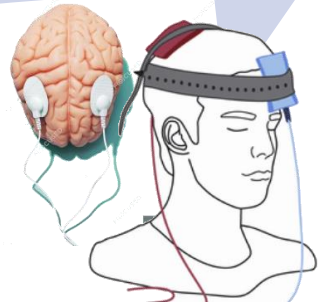
Non-Pharmachological therapies

Luigi Galvani (1727-1798) -> Giovanni Aldini







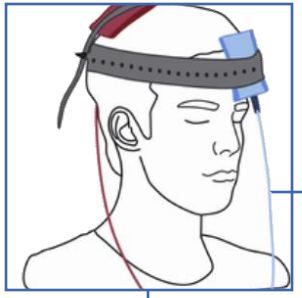


- Tsoucalas, G et al. 2014. The "torpedo" effect in medicine
- Stagg C, Nitsche M. 2011. Physiological basis of transcranial direct current stimulation

Non-invasive Brain stimulation techniques

TMS

- Magnetic fields -> neuron stimulation
- FDA-Approved
  - Depression (2008)
  - Migraine Pain (2013)
  - Obsessive Compulsive Disorder (2018)



tDCS

- Weak Electrical current
- Minor, focal side effects
- Only approved for research use

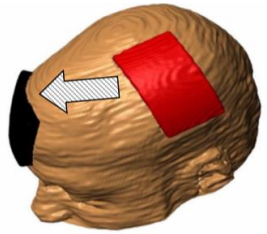
Commissioner, O. (2018, August 17). FDA permits marketing of transcranial magnetic stimulation for treatment of obsessive-compulsive disorder. Retrieved February 02, 2022,
Kvašňák, E., & Rokyta, R. (2018). Brain stimulation methods for pain treatment. *General physiology and biophysics*, *37*(5), 477–494.

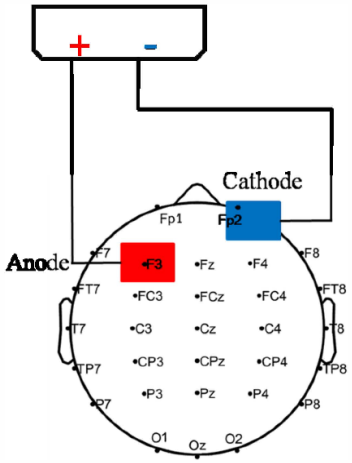
Transcranial Direct Current Stimulation (tDCS)

- Simple, safe and powerful non-invasive neuromodulation technique.
- Modulates spontaneous neuronal activity
- Applies **weak** constant electric current (2mA or less) via two electrodes over the scalp

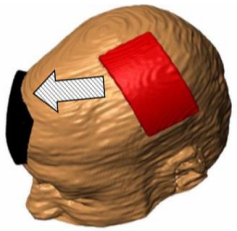
Characteristics:

- Non-expensive
- Portable
- Easy to provide
- Few adverse effects





tDCS combined with other techniques



+

exercise

yoga

Cognitive therapies

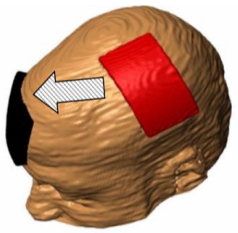
Meditation techniques

Physical Rehabilitation

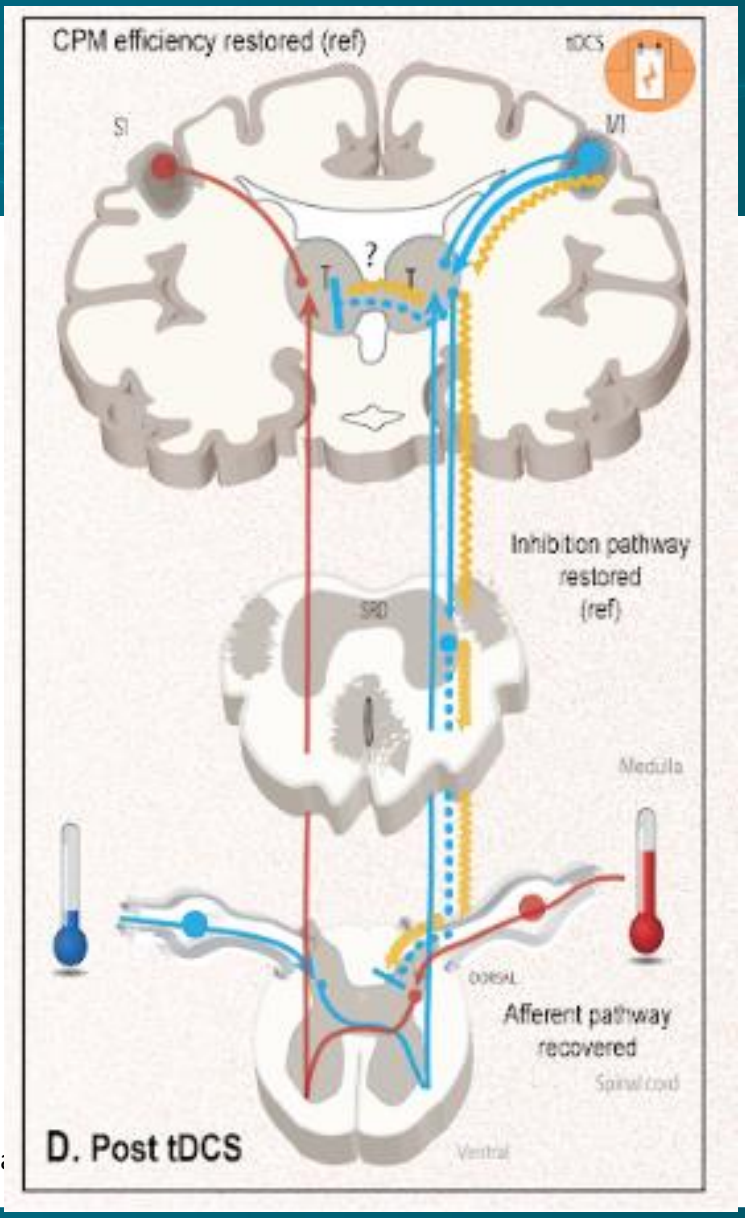
Home based tDCS – potential

Home-based tDCS tutorial. Source: Spaulding Neuromodulation Center

Motor cortex stimulation and Pain



Motor cortex

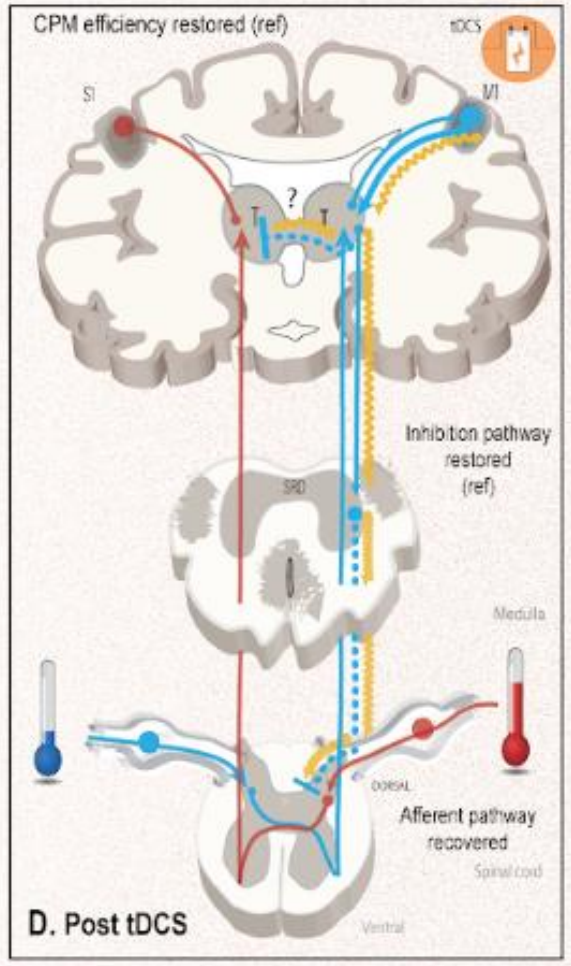


Duarte D, Castelo-Brando LEC, Uygur Kucukseyman E, Fregni F. Developing an optimized strategy with transcranial direct current stimulation to enha
the endogeneous pain control system in fibromyalgia. Expert Review of Medical Devices, 15:12, 863-873.

Motor cortex stimulation and Pain

- Boggio et al. 2008, showed that active M1 tDCS **increased the sensory and pain thresholds** compared sham tDCS.

- Clinical effects of tDCS on fibromyalgia, two recent meta-analysis **showed statistically significant results with moderate effect sizes.**



Boggio PS et al, 2008. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol. 2(
Duarte D, Castelo-Brando LEC, Uygur Kucukseyman E, Fregni F. Developing an optimized strategy with transcranial direct current stimulation to enhance the endog
system in fibromyalgia. Expert Review of Medical Devices, 15:12, 863-873.

Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders

Pain

Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/tasks	Results	Class
Neuropathic pain								
Boggio et al. (2009)	8	C3/C4 on side opposite to max pain	Contralateral SO	0.571, 30 min	$1^{+aaT,asT,ssT}$	TENS (active/sham)	Positive (VAS)	III
Jensen et al. (2013)	30	C3/C4 on side opposite to max pain	Contralateral SO	0.571, 20 min	$1^{+as,h,m,n}$	No	Negative (NRS pain—current, least, worst, average)	III
Li et al. (2018)	12	C3	Contralateral SO	0.571, 20 min	1^{+as}	Breathing-controlled electrical stimulation (BreEStim) to median nerve on dominant side	Negative (VAS)	III
O'Neill et al. (2018)	21	Contralateral SO	C3/C4 on side opposite pain	0.560, 20 min	5^{+acs}	No	Negative (NRS daily pain)	III
O'Neill et al. (2018)	21	C3/C4 on side opposite pain	Contralateral SO	0.560, 20 min	5^{+acs}	No	Negative (NRS daily pain)	III
Wrigley et al. (2013)	10	C3/C4 based on dominant hemisphere	Contralateral SO	0.571, 20 min	5^{+as}	No	Negative (NPS)	III
Attal et al. (2016)	35	C3/C4 on side opposite max pain	Contralateral SO	0.571, 30 min	$3^{+as\ (nested\ parallel\ trial,\ tDCS,\ rTMS)}$	No	Negative (BPI)	III
Fregni et al. (2006f)	17	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS)	II
Soler et al. (2010)	39	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	10	Visual illusion/control illusion	Positive (combined group: NRS overall, continuous, paroxysmal; tDCS group: NRS paroxysmal)	II
Bae et al. (2014)	14	C3/C4 opposite to hemiplegic side	Contralateral SO	0.571, 20 min	9 (3/wk × 3 wk)	No	Positive (VAS)	II
Thibaut et al. (2017)/ Phase I	33	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS average, VAS least), Negative (VAS present, VAS worst)	II
Thibaut et al. (2017)/ Phase 2	9	C3/C4 on side opposite max pain	Contralateral SO	0.571, 20 min	5	No	Positive (VAS average), Negative (VAS least, VAS present, VAS worst)	II
Lewis et al., (2018)	30	C3/C4 on side opposite affected upper limb	Contralateral SO	0.286, 20 min	5	No	Negative (BPI, SF-MPQ2)	II

Recommendation: anodal M1 tDCS probably effective in reducing neuropathic pain (Level B)

Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders

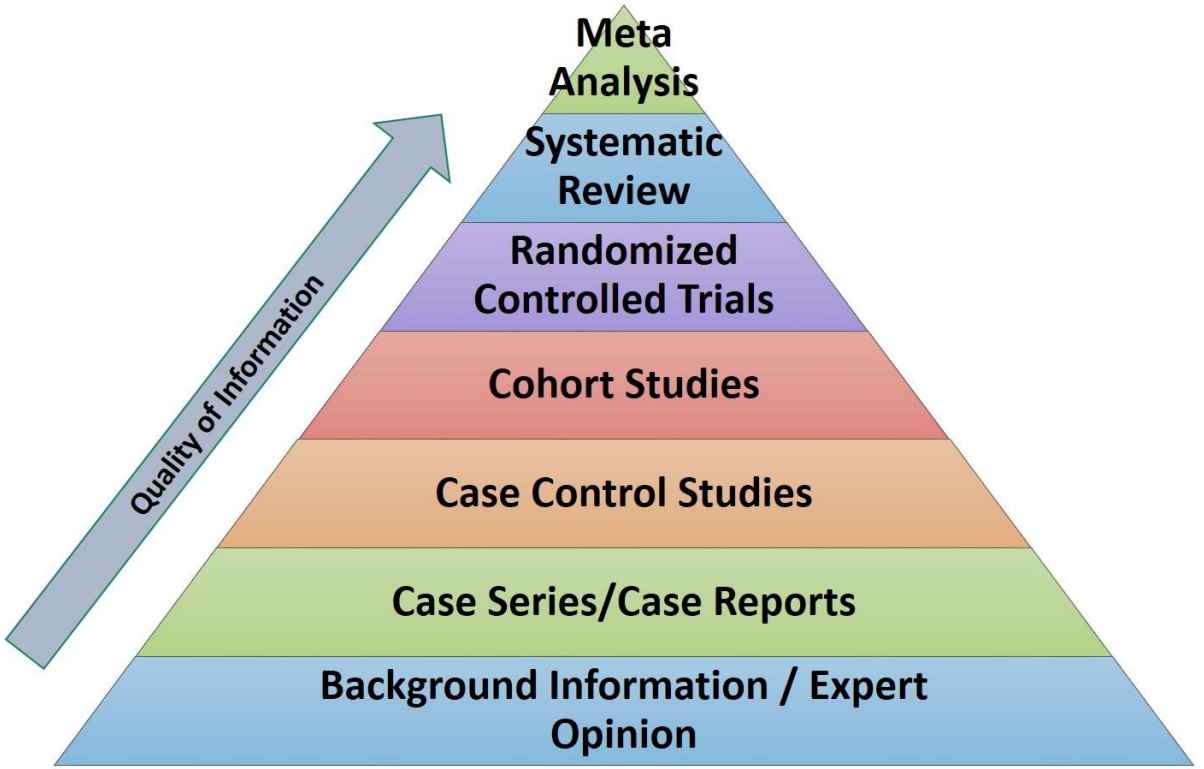
Author	Sample (n)	Anode	Cathode	Current density (A/m²), duration	Number of sessions	Concomitant therapy/tasks	Results	Class
Fibromyalgia								
Villamar et al. (2013)	18	C3	Cz, F3, T7, P3	1.000, 20 min	1[+acs]	No	Positive (VNS)	III
Mendonca et al. (2011)[a]	30	C3	Cervicothoracic	1. 250, 20 min	1	No	Negative (VNS)	II
Mendonca et al. (2011)[a]	30	Cervicothoracic	C3	1. 250, 20 min	1	No	Negative (VNS)	II
Mendonca et al. (2011)[a]	30	Right SO	Cervicothoracic	1. 250, 20 min	1	No	Positive (VNS)	II
Mendonca et al. (2011)[a]	30	Cervicothoracic	Right SO	1. 250, 20 min	1	No	Positive (VNS)	II
Fregni et al. (2006e)[a]	32	F3	Contralateral SO	0.571, 20 min	5	No	Negative (VAS)	II
To et al. (2017)[a]	42	Left occipital (nerve)	Right occipital (nerve)	0.429, 20 min	8 (2/wk×4 wk)	No	Positive (NRS)	II
To et al. (2017)[a]	42	F3	F4	0.429, 20 min	8 (2/wk×4 wk)	No	Positive (NRS)	II
Fregni et al. (2006e)[a]	32	C3	Contralateral SO	0.571, 20 min	5	No	Positive (VAS)	II
Riberto et al. (2011)	23	C3	Contralateral SO	0.571, 20 min	10 (1/wk×10 wk)	Pain rehab program	Positive (SF-36 pain), Negative (VAS)	II
Fagerlund et al. (2015)	48	C3	Contralateral SO	0.571, 20 min	5	No	Positive (NRS)	II
Mendonca et al. (2016)	45	C3	Contralateral SO	0.571, 20 min	5	Aerobic exercise	Positive (VNS)	II
Khedr et al. (2017a)	36	C3	Contralateral arm	0.833, 20 min	10	No	Positive (VAS)	II

Recommendation: anodal M1 tDCS probably effective in reducing fibromyalgia pain (Level B); no recommendation for other montages

Fregni F et al. Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders. Int J Neuropsychopharmacol. 2021 Apr 21

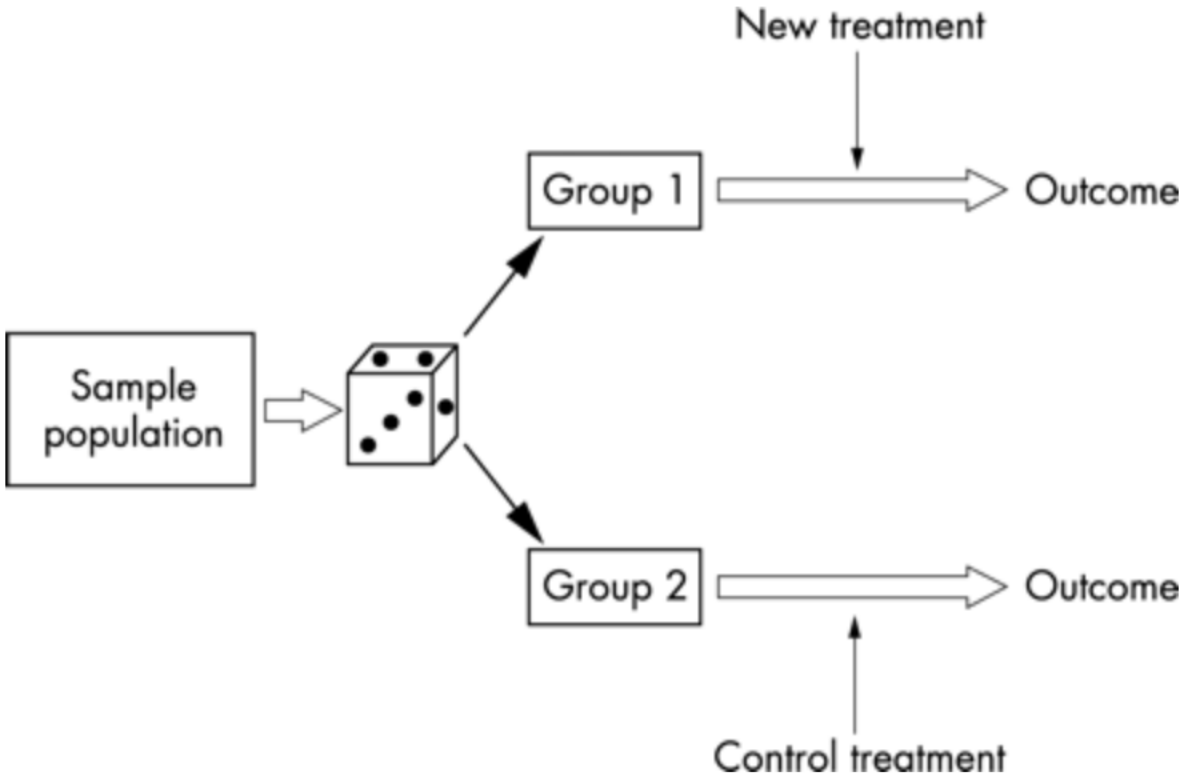
Importance of research and RCTs

- Chronic Pain
  - Common pain medication including Opioids commonly not effective + have too many side effects
  - Effective non-pharmacological approaches are needed
- Randomized clinical trials are one of the top study types considered when approving a new treatment
- Science-based foundation for clinical conduct



Becker, W. C., Dorflinger, L., Edmond, S. N., Islam, L., Heapy, A. A., & Fraenkel, L. (2017). Barriers and facilitators to use of non-pharmacological treatments in chronic pain. *BMC family practice*, *18*(1), 1-8.
Novitzke J. M. (2008). The significance of clinical trials. *Journal of vascular and interventional neurology, 1*(1), 31.

Randomized Clincial Trials

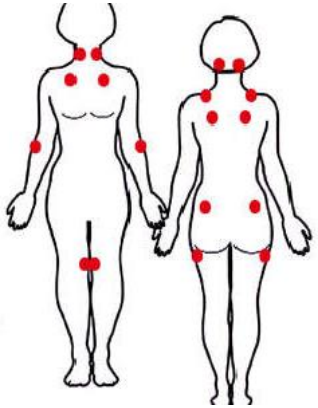


Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emergency Medicine Journal* 2003;**20:**164-168.

Randomized Clinical Trial

Fibromyalgia

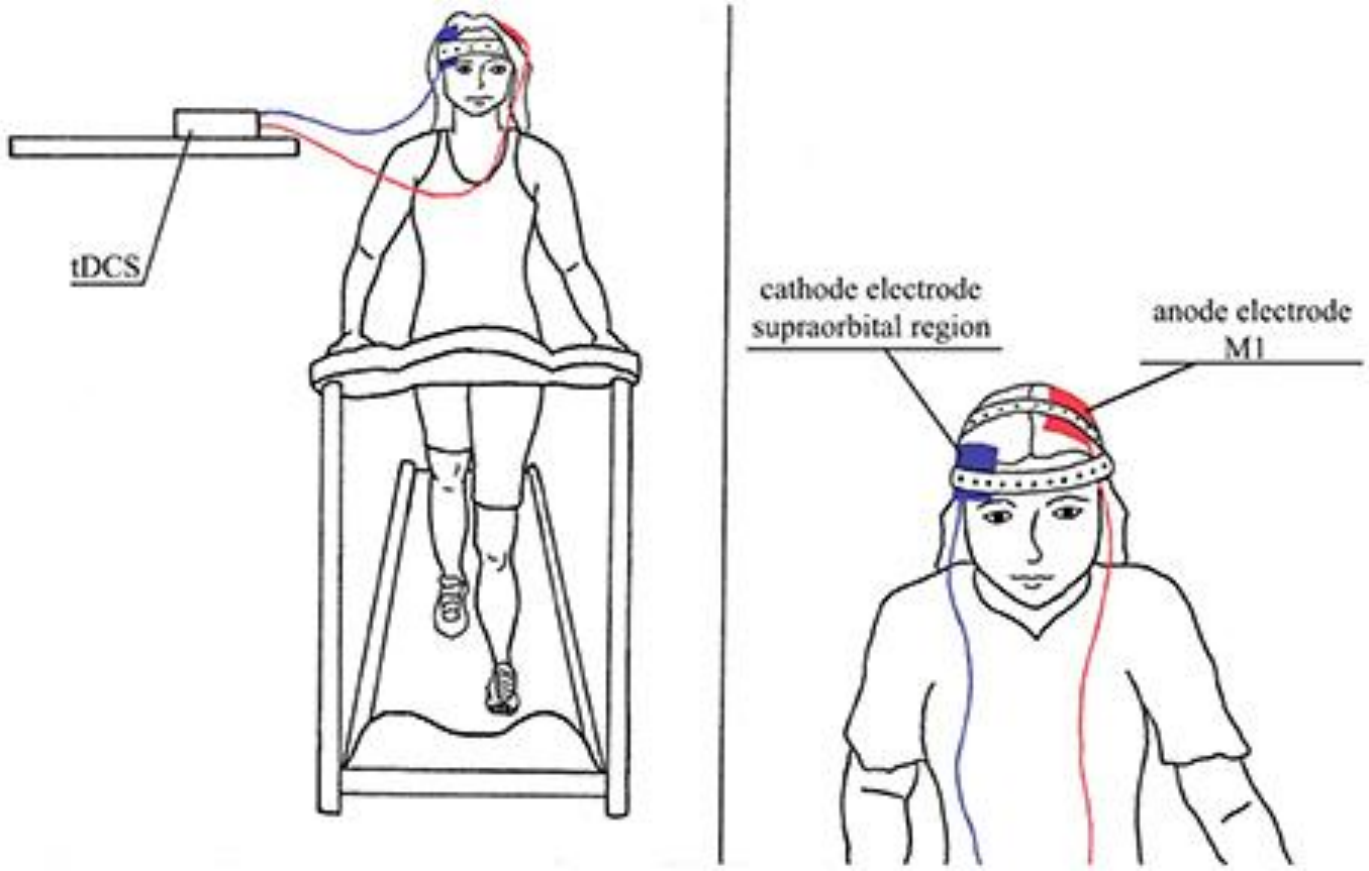
- Affects upwards 5 million people anually in the US.
- Main characteristic: **widespread pain.**
- Has a considerable impact on tha daily life routines.
- Common treatment: sides effects and poor rates of success.
- Etiology unknown, but some evidence suggest a d**eficit in the endogeneous pain control system leading to chronic pain.**



ClinicalTrials.gov Identifier: NCT03371225

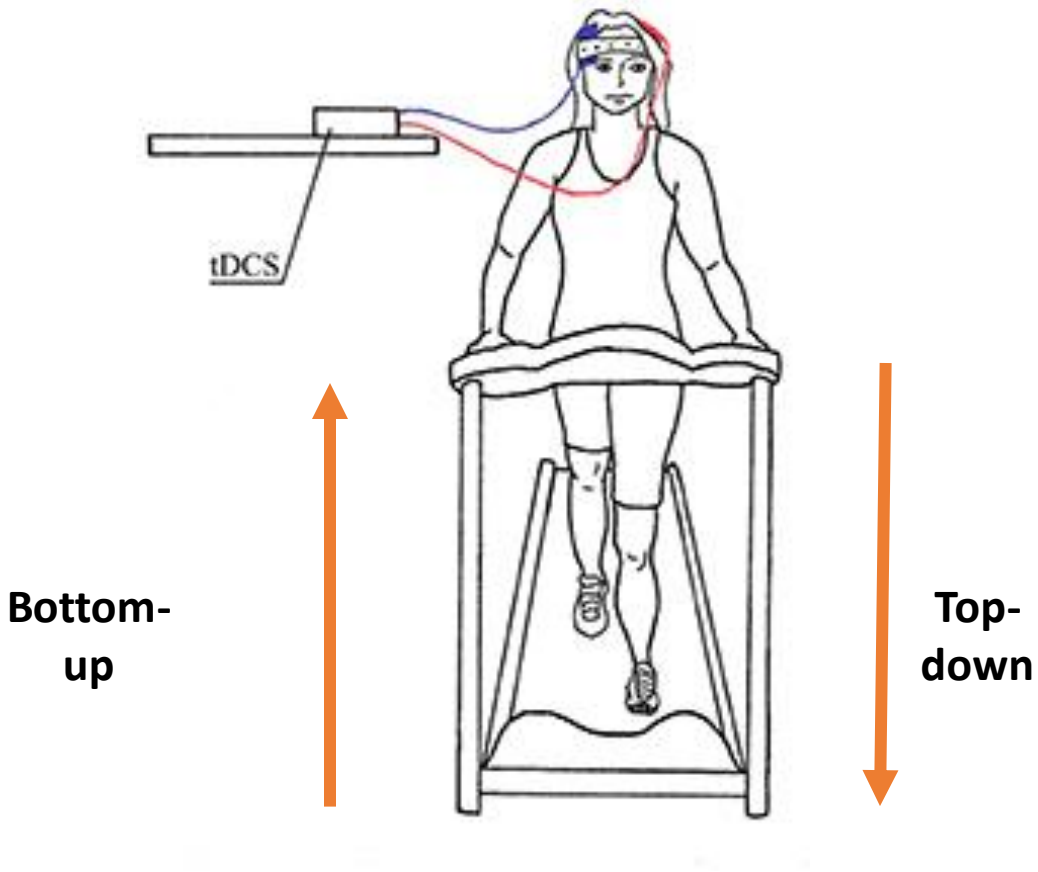
Interventions

Optimized tDCS combined with aerobic exercise



Exercise´s effects on pain

- Exercise is able to enhanced the endogeneous pain control system by the production of endorphines.



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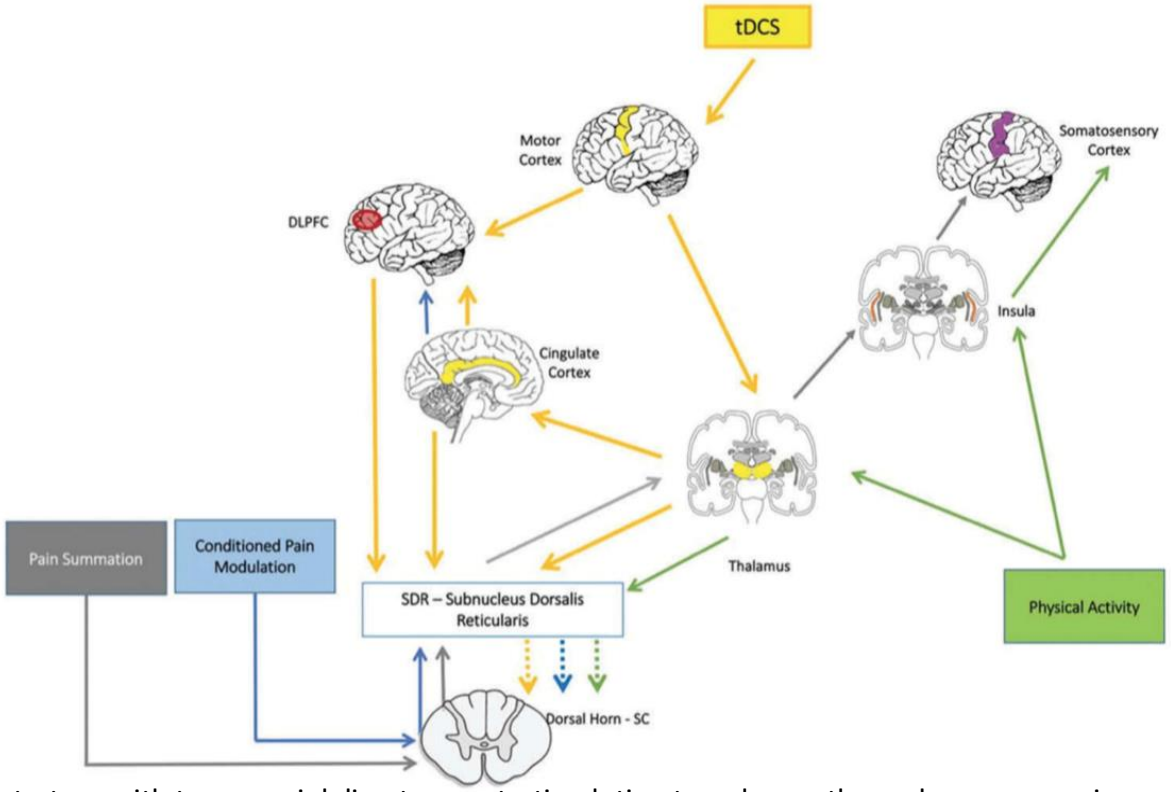
Neural mechanisms of combined tDCS and exercise

- Bottom-up effect elicited by aerobic exercise.
- Top-down enhancement by tDCS.
- Mendonça et al. obtained **positive and moderate effects on pain relief** quality of life and anxiety by combining tDCS and aerobic exercise in fibromyalgia.



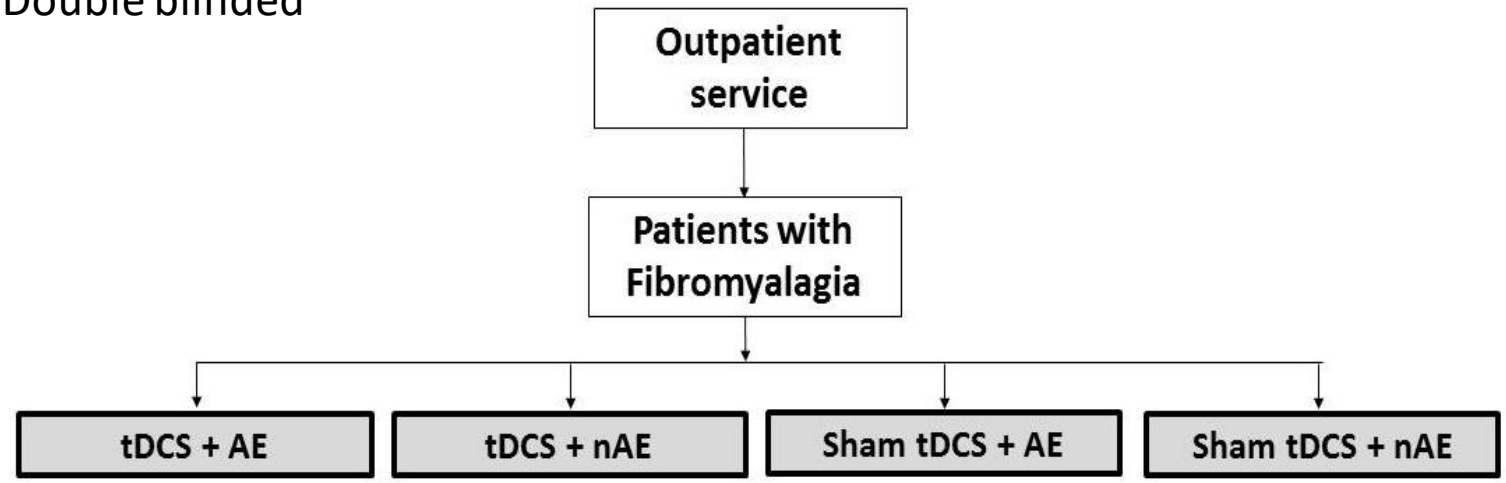
1. Duarte D, Castelo-Brando LEC, Uygur Kucukseyman E, Fregni F. Developing an optimized strategy with transcranial direct current stimulation to enhance the endogeneous pain control system in fibromyalgia. Expert Review of Medical Devices, 15:12, 863-873.
2. Mendoça ME, Simis M, Collange L et al. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo controlled clinical trial. Front Hum Neurosci. 2016;10.

Optimized tDCS for fibromyalgia: targeting the endogenous pain system

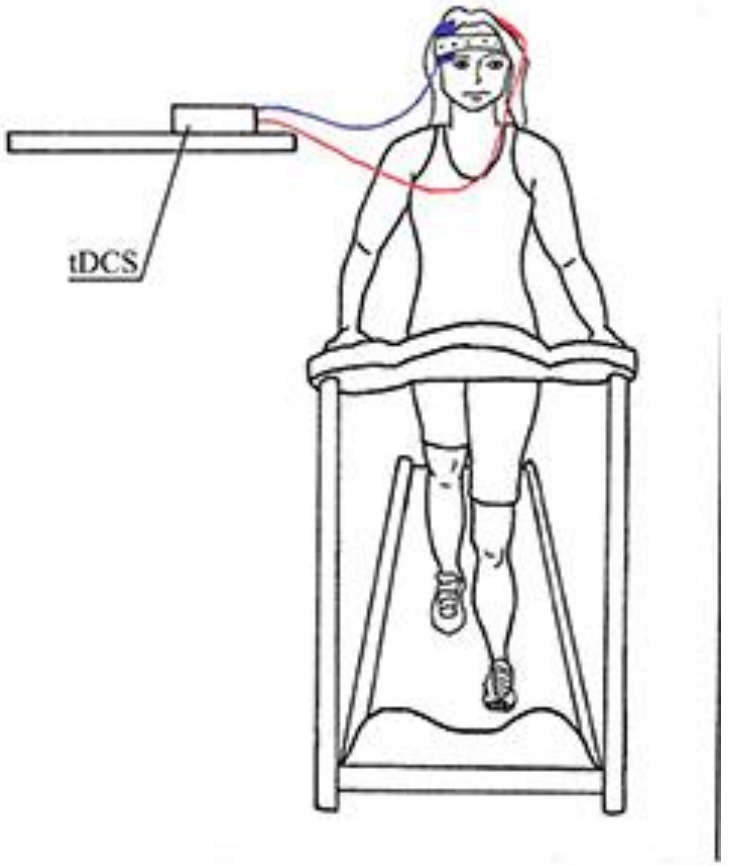
Fibromyalgia is related to deficits in the endogenous pain control system
tDCS + exercise: Novel non-pharmacological therapy that modulates cortical excitability and modify the activity of the CNS

Safe, cost-effective, minimal side-effects

Double blinded

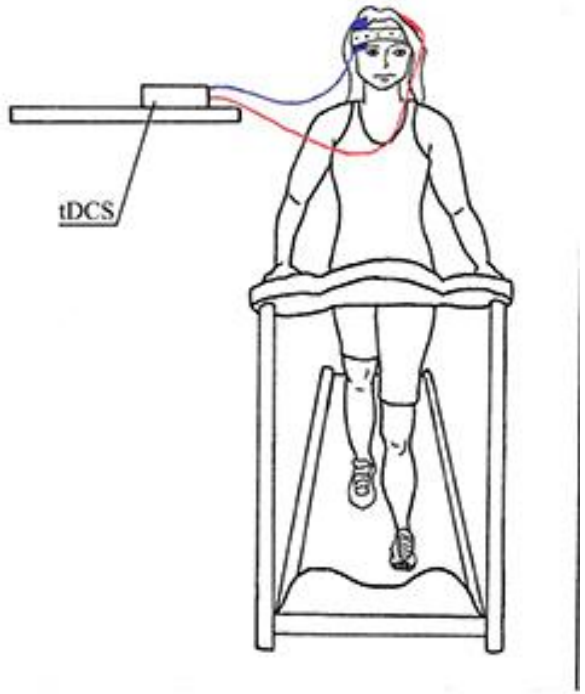


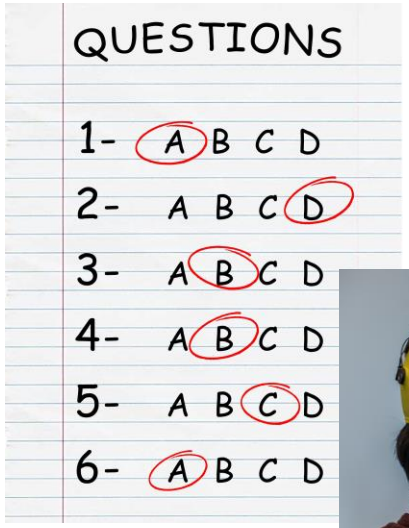
Factorial design: 1:1:1:1 allocation in 4 groups



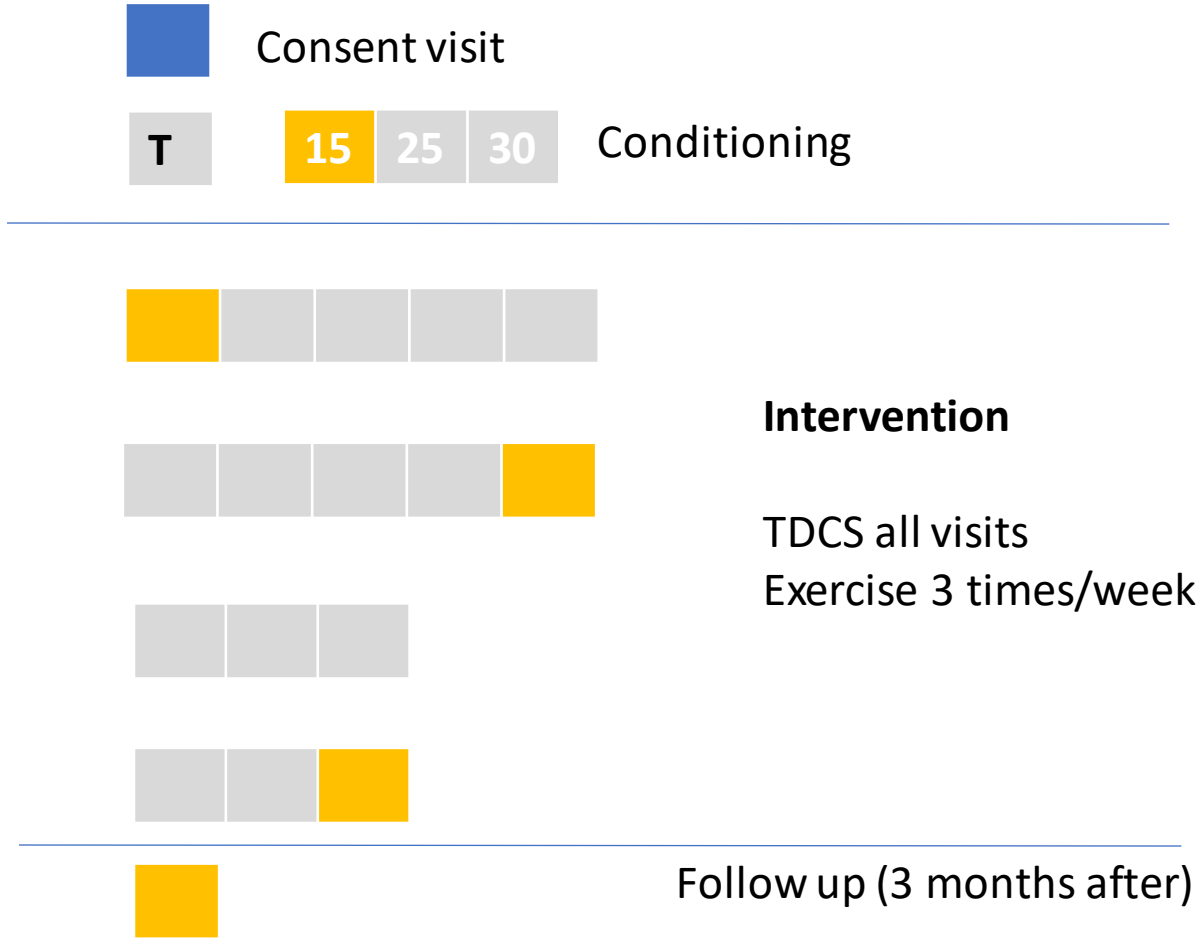
ClinicalTrials.gov Identifier: NCT03371225

Intervention + Assessments



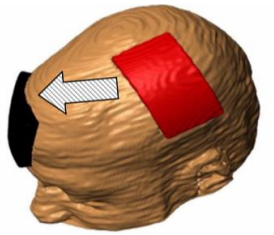


- First visit: Consent visit
- 22 visits:
- 16 sessions of tDCS
  - Anode Left motor cortex
  - Cathode in SO
  - 2mA for 20 minutes
- 12 sessions of Exercise
  - 30 minutes



Importance

- To contribute with insightful information to field.
- To provide a potential treatment for chronic pain that is:
  - Relatively inexpensive
  - Easy to provide (home based devices)
  - Few side effects



SPAULDING
NEUROMODULATION CENTER

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