

NEURAL SIGNATURES OF CHRONIC PAIN

THE POTENTIAL OF NEUROMODULATION

Rodrigo Pegado, PHT, MSc, PhD.



Objectives of the conference

Present recent advances in the study of **central pain mechanisms**.

Improve understanding of the **neural signatures of pain**.

Explore how these findings may contribute to improving the **assessment, understanding, and management** of chronic pain.



1 MECHANISM

- Maladaptive neuroplasticity
- Central sensitization
- Descending modulation



2 CLINICAL PRACTICE

- Targets
- Evidences
- Populations



3 HEALTH AND WELL-BEING

- Emotional
- Physical
- Inclusion

Chronic pain as a leading cause of disability

The overall unweighted prevalence of reported pain is 28%.

Zimmer et al. *Pain*. 2022 01; 163(9): 1740–1750.

The Global Burden of Disease Study 2013 evaluated years lived with disability (YLDs).

Chronic low back pain was identified as the single greatest cause of YLDs worldwide.

Other high-burden pain conditions include... →

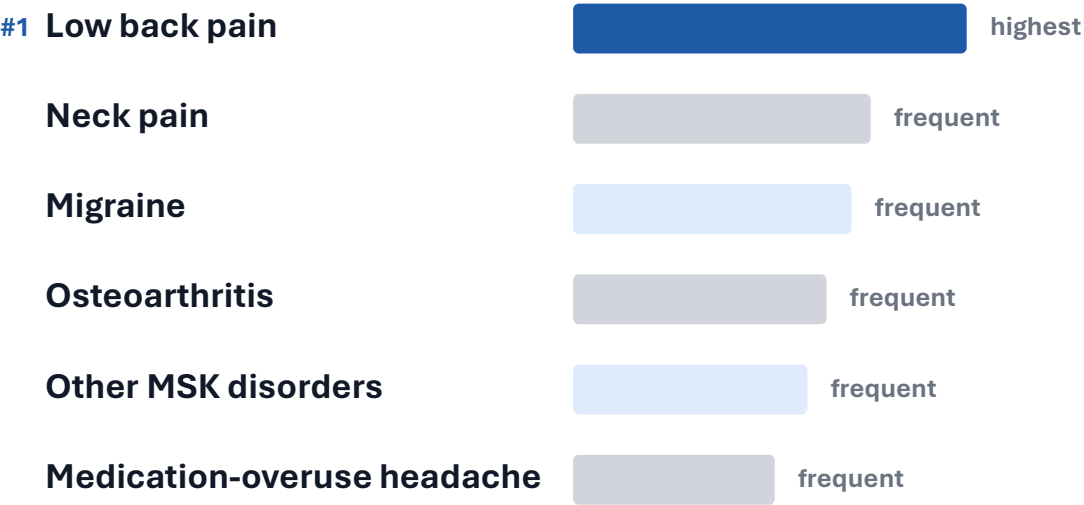
Interpretation

Chronic Pain is not only a symptom, it is a major driver of disability, health service demand, and long-term functional limitation.



Pain-related contributors to YLDs

Global Burden of Disease Study 2013

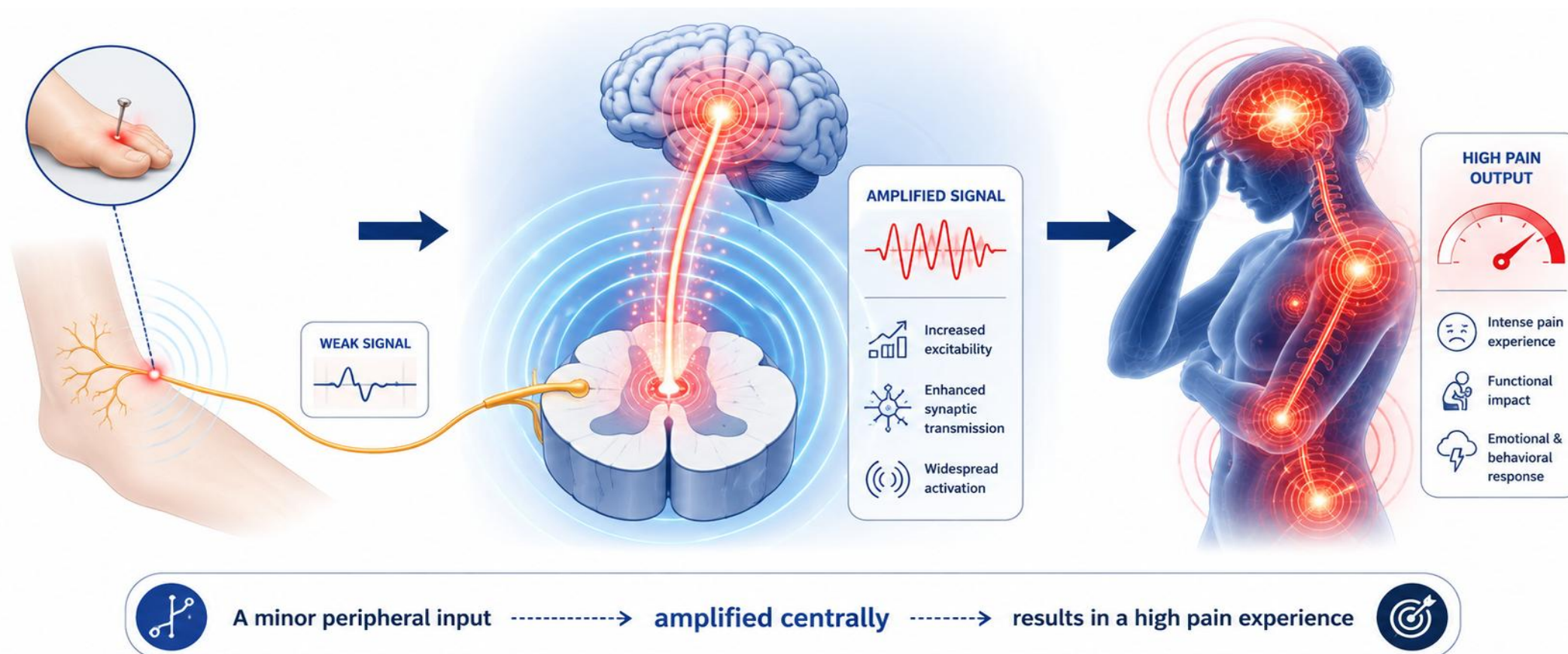




Central sensitization

Central neurons become more responsive to incoming stimuli, producing a disproportionate output for a relatively small peripheral input.

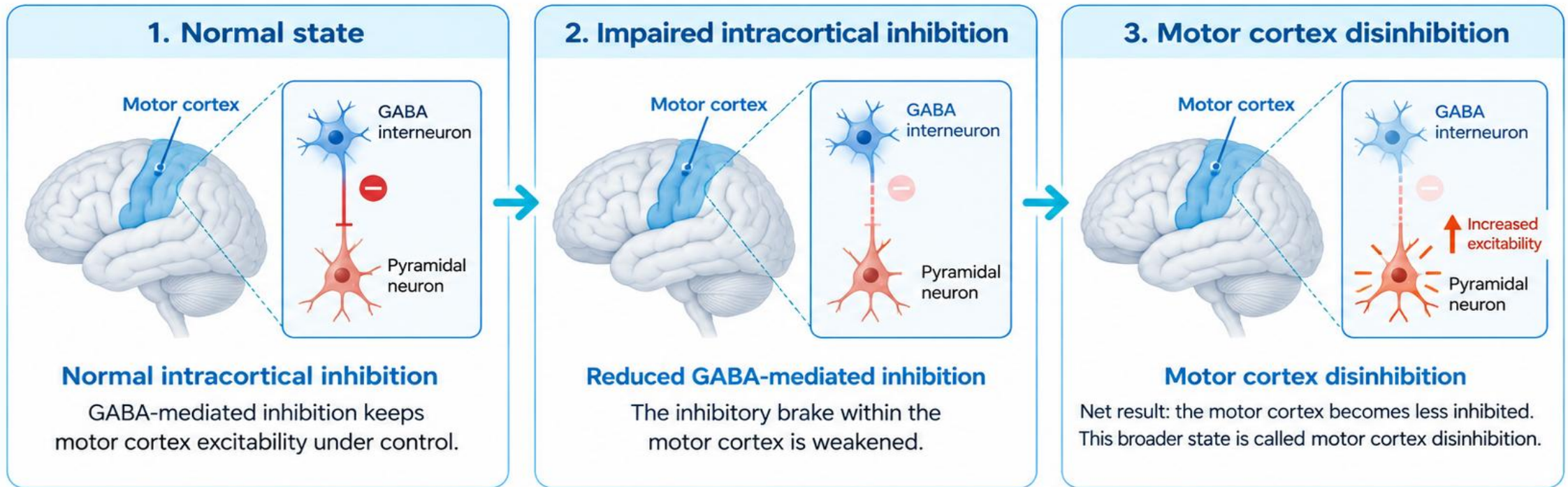
Bai et al. *Nature Mental Health* | Volume 2 | May 2024 | 496–513



Motor cortex disinhibition

Chronic pain is not just persistent input; it reflects maladaptive neuroplasticity.

Parker et al. Brain Stimulation | May 2016



Clinical expression

1. Reduced physical activity; increased sedentary behavior and kinesiophobia.

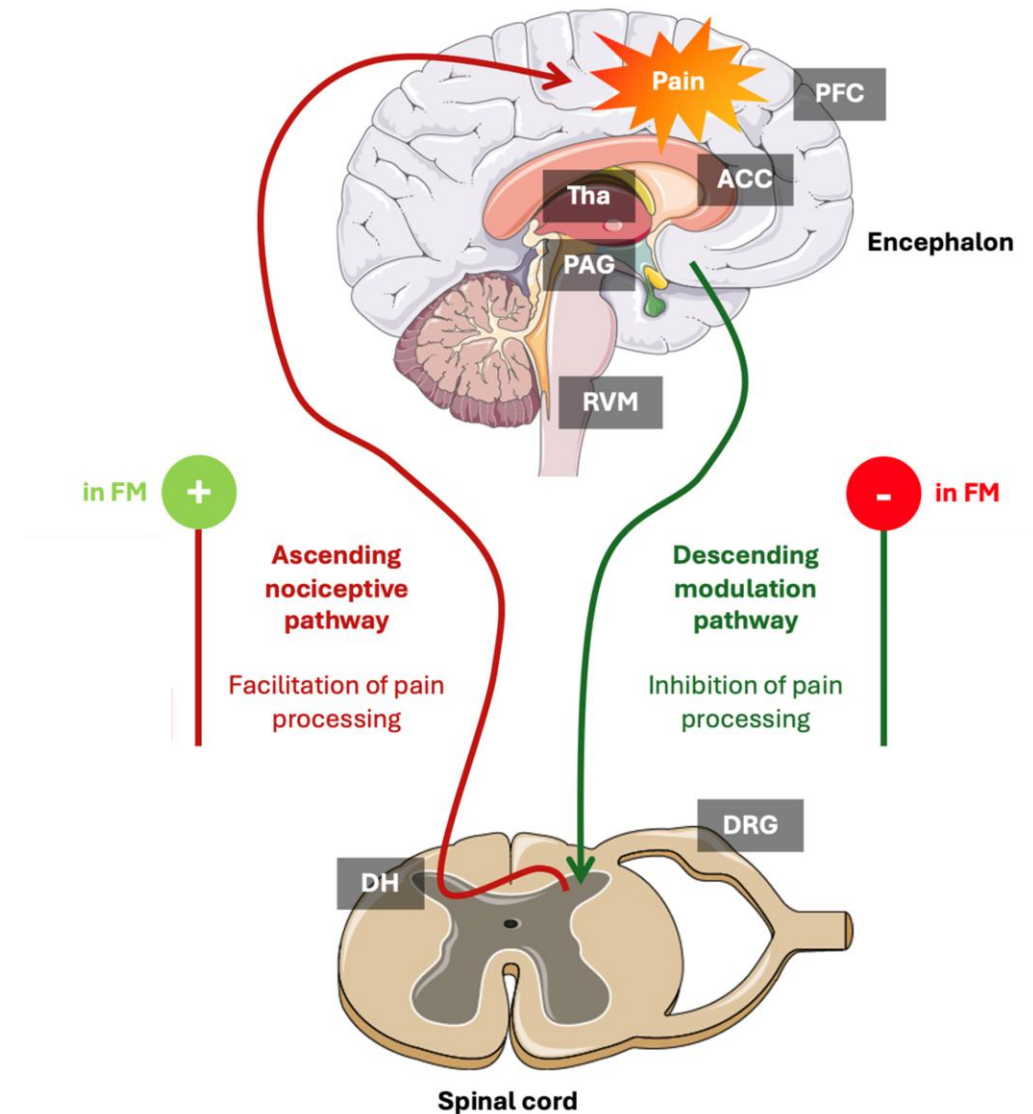
MECHANISM 3

Loss of balance in descending modulation

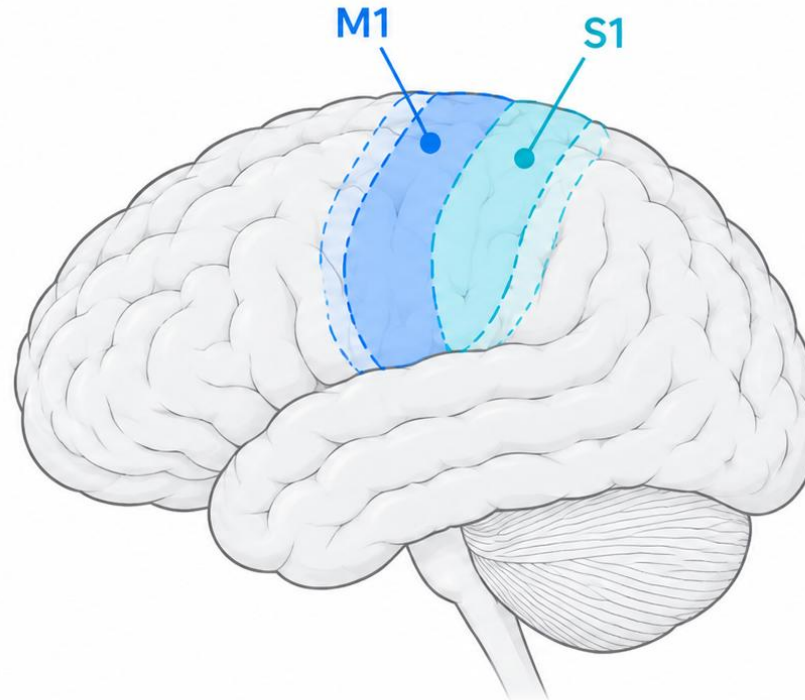
Carneiro et al. Diagnostics | 2025

Persistent pain may shift the descending system toward less inhibition and more facilitation of nociceptive signaling.

Fibromyalgia →



reorganisation of the primary motor and sensory cortices



Reported in:

Phantom limb pain

Back pain

Carpal tunnel syndrome

Osteoarthritis

Complex regional pain syndrome (CRPS)

The extent of motor cortex reorganisation is positively associated with chronic pain intensity

Cortical reorganisation is thought to be initiated by changes in intracortical excitability

Parker et al. Brain Stimulation | May 2016

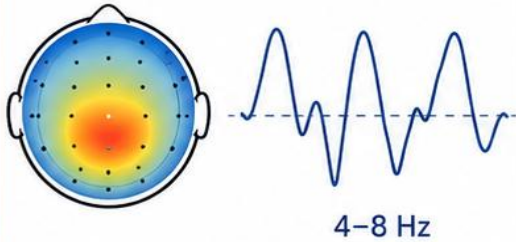
► PLoS One. 2016 Feb 25;11(2):e0149085. doi: [10.1371/journal.pone.0149085](https://doi.org/10.1371/journal.pone.0149085) 

Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature

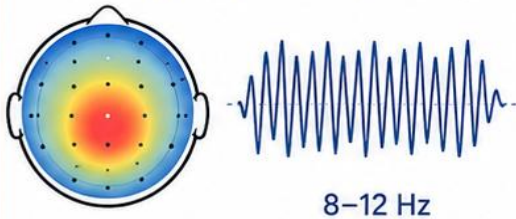
[Eulália Silva dos Santos Pinheiro](#)^{1,2,#}, [Fernanda Costa de Queirós](#)^{2,#}, [Pedro Montoya](#)^{3,#}, [Cleber Luz Santos](#)²,
[Marion Alves do Nascimento](#)^{1,2}, [Clara Hikari Ito](#)^{1,2}, [Manuela Silva](#)^{1,2}, [David Barros Nunes Santos](#)^{2,#}, [Silvia](#)
[Benevides](#)^{2,4}, [José Garcia Vivas Miranda](#)⁵, [Katia Nunes Sá](#)^{2,6}, [Abrahão Fontes Baptista](#)^{1,2,6,*,#}

1 Resting EEG

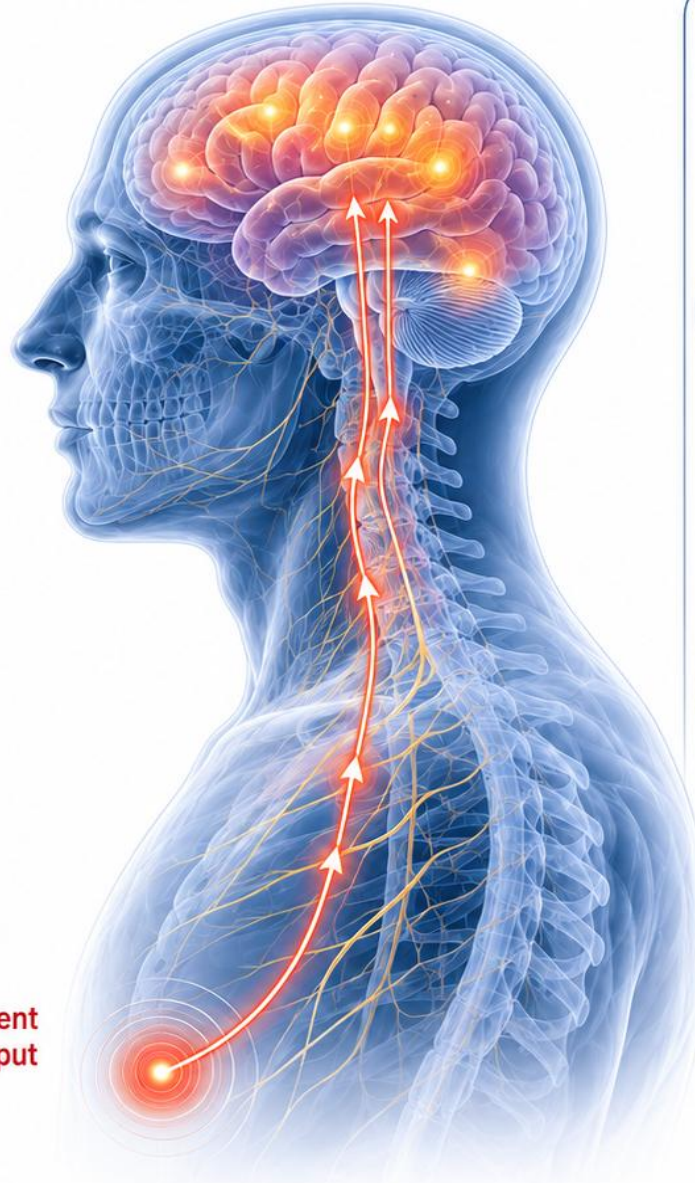
Theta power ↑



Alpha power ↑

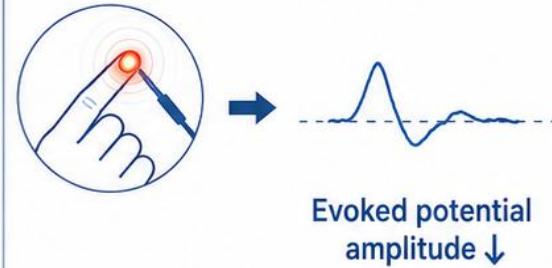


Persistent
pain input

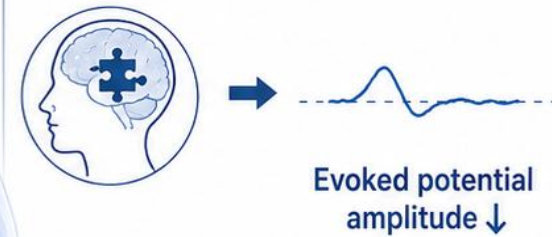


2 After sensory stimulation and cognitive tasks

Sensory stimulation



Cognitive task

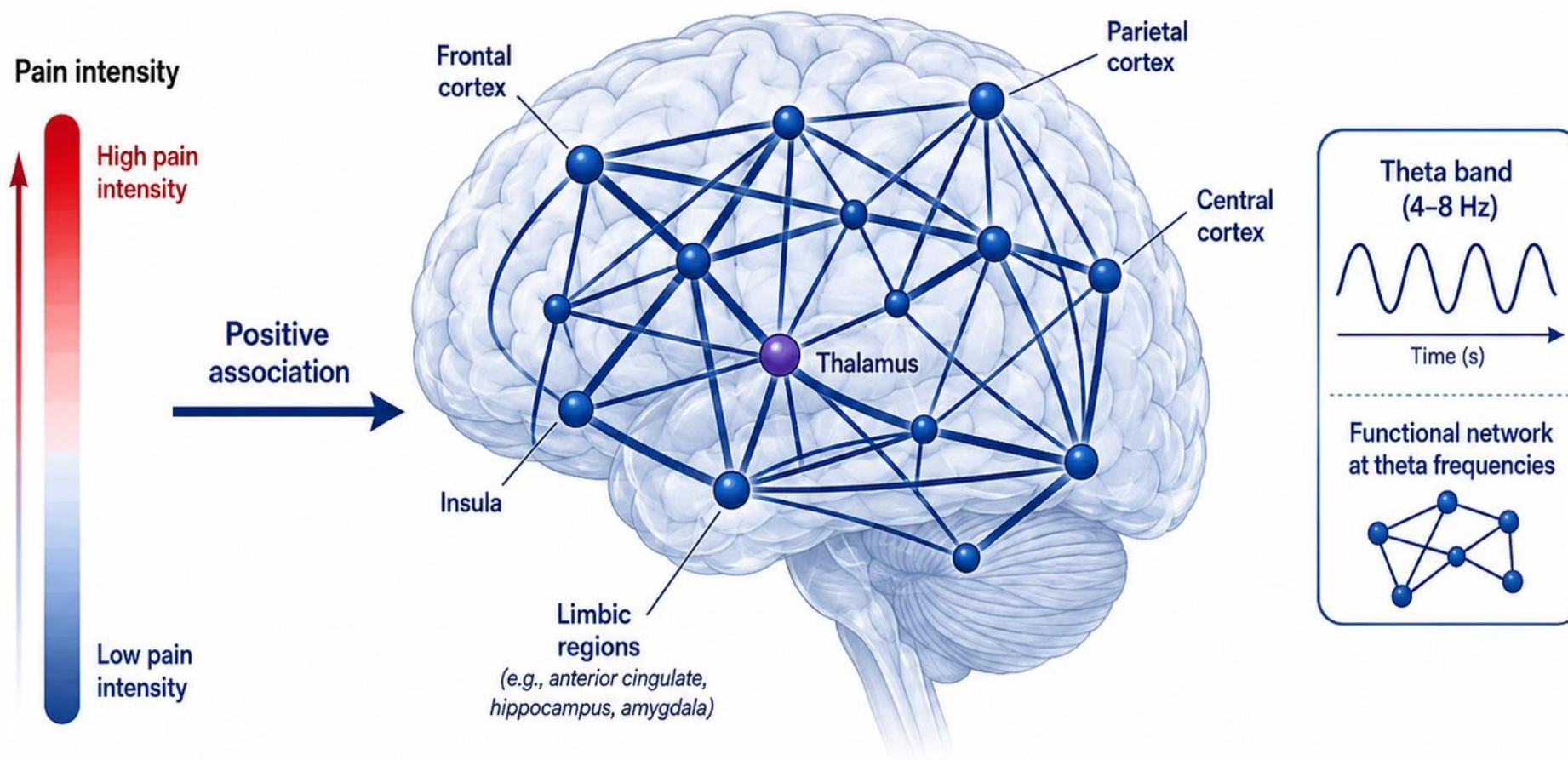


- Enhanced brain oscillatory activity
- Persistent nociceptive signaling

Exploring electroencephalographic chronic pain biomarkers: a mega-analysis

[Felix S. Bott](#)^{a,b,c} · [Paul Theo Zebhauser](#)^{a,b,c} · [Vanessa D. Hohn](#)^{a,b} · [Özgün Turgut](#)^d · [Elisabeth S. May](#)^{a,b,c} ·
[Laura Tiemann](#)^{a,b,c} · [Cristina Gil Ávila](#)^{a,b} · [Henrik Heitmann](#)^{b,c} · [Moritz M. Nickel](#)^{a,b} · [Melissa A. Day](#)^e · [Divya B. Adhia](#)^f ·
[Yoni K. Ashar](#)^g · [Tor D. Wager](#)^h · [Yelena Granovsky](#)ⁱ · [David Yarnitsky](#)ⁱ · [Mark P. Jensen](#)^j · [Joachim Gross](#)^k ·
[Markus Ploner](#)^{a,b,c}   [Show less](#)

614 individuals with chronic pain, collected by research groups from Australia, Germany, Israel, New Zealand, and the US.



KEY MESSAGE

Higher pain intensity is associated with greater brain network connectivity at theta frequencies.

EEG theta and beta bands as brain oscillations for different knee osteoarthritis phenotypes according to disease severity

Marcel Simis^{1,5}, Marta Imamura^{1,5}, Kevin Pacheco-Barrios^{2,3,5}, Anna Marduy², Paulo S. de Melo², Augusto J. Mendes^{2,4}, Paulo E. P. Teixeira², Linamara Battistella¹ & Felipe Fregni²✉

Scientific Reports | (2021) 11:24011

Thalamocortical dysrhythmia, which is thought to arise from abnormal oscillatory activity and to contribute to the amplification and persistence of pain.

Impaired neuronal inhibition, with reduced cortical inhibitory activity being associated with greater functional impairment.

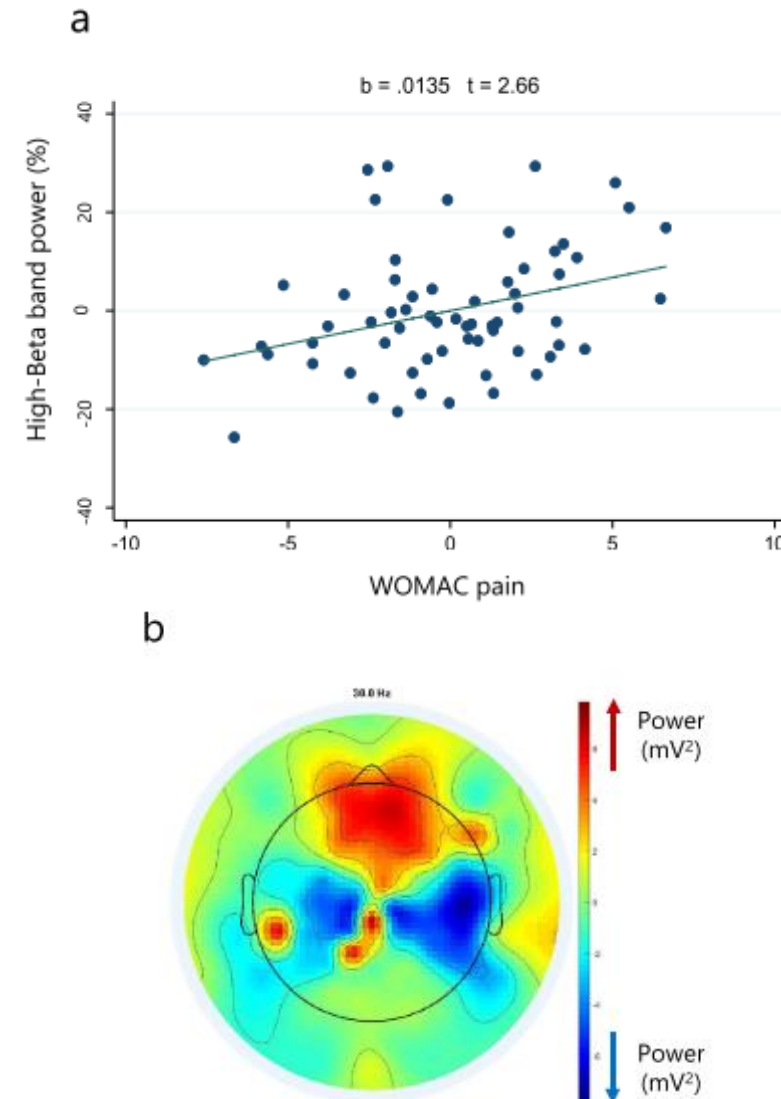
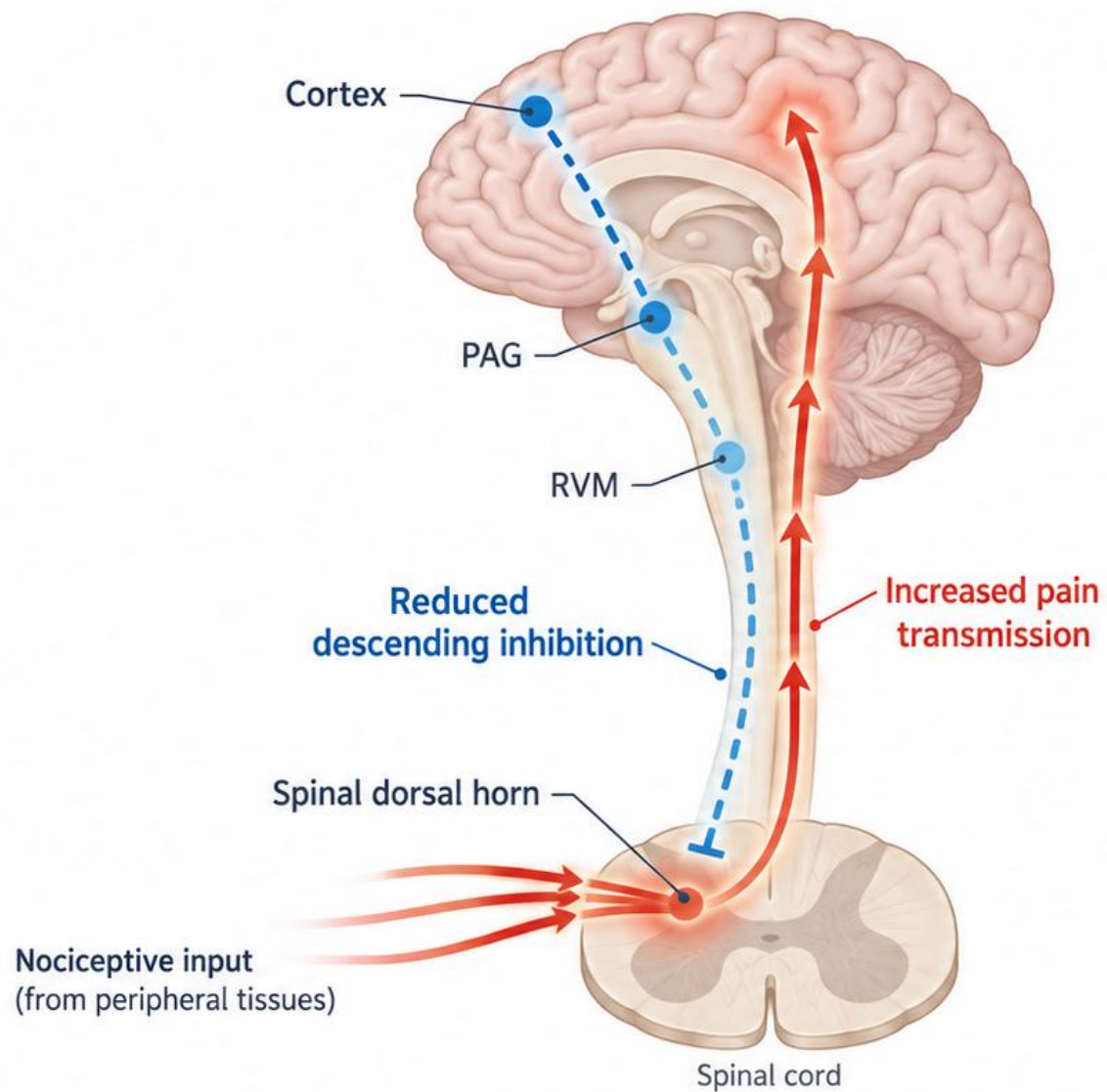


Figure 2. (a) High-beta band power and pain intensity adjusted correlation (from multivariate model of frontal region). (b) Topographical plot of spectral power from representative subjects ($n = 15$) with high pain intensity (higher than 10 in WOMAC pain scale).



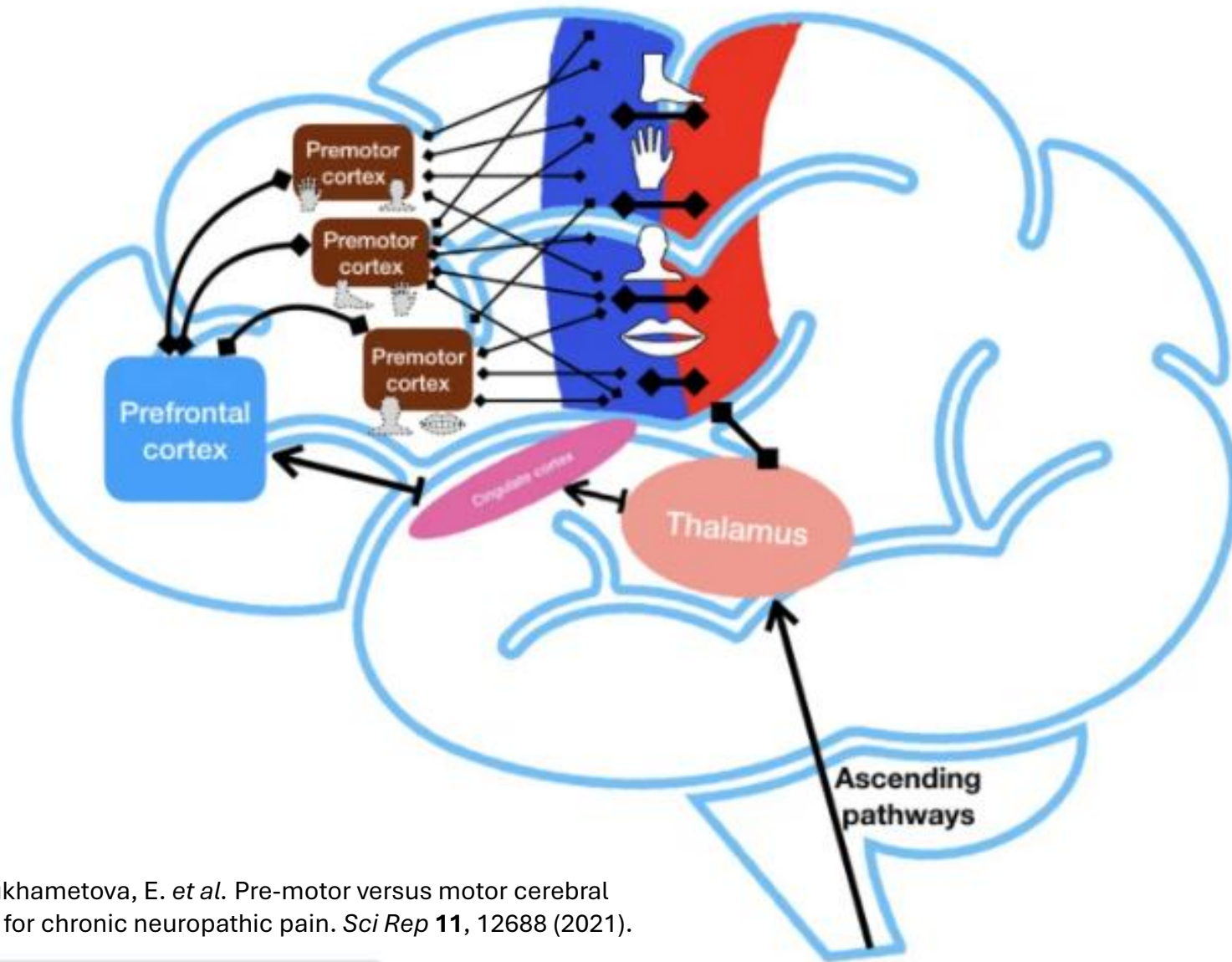
Reduced endogenous pain control



Less inhibition at the spinal dorsal horn



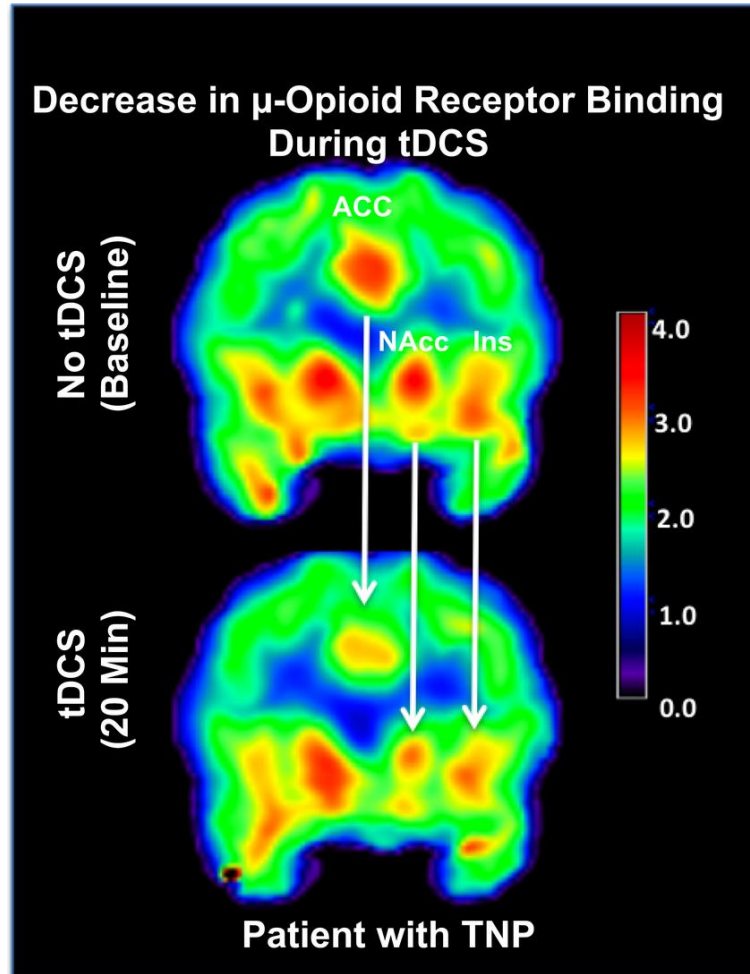
Persistent pain amplification



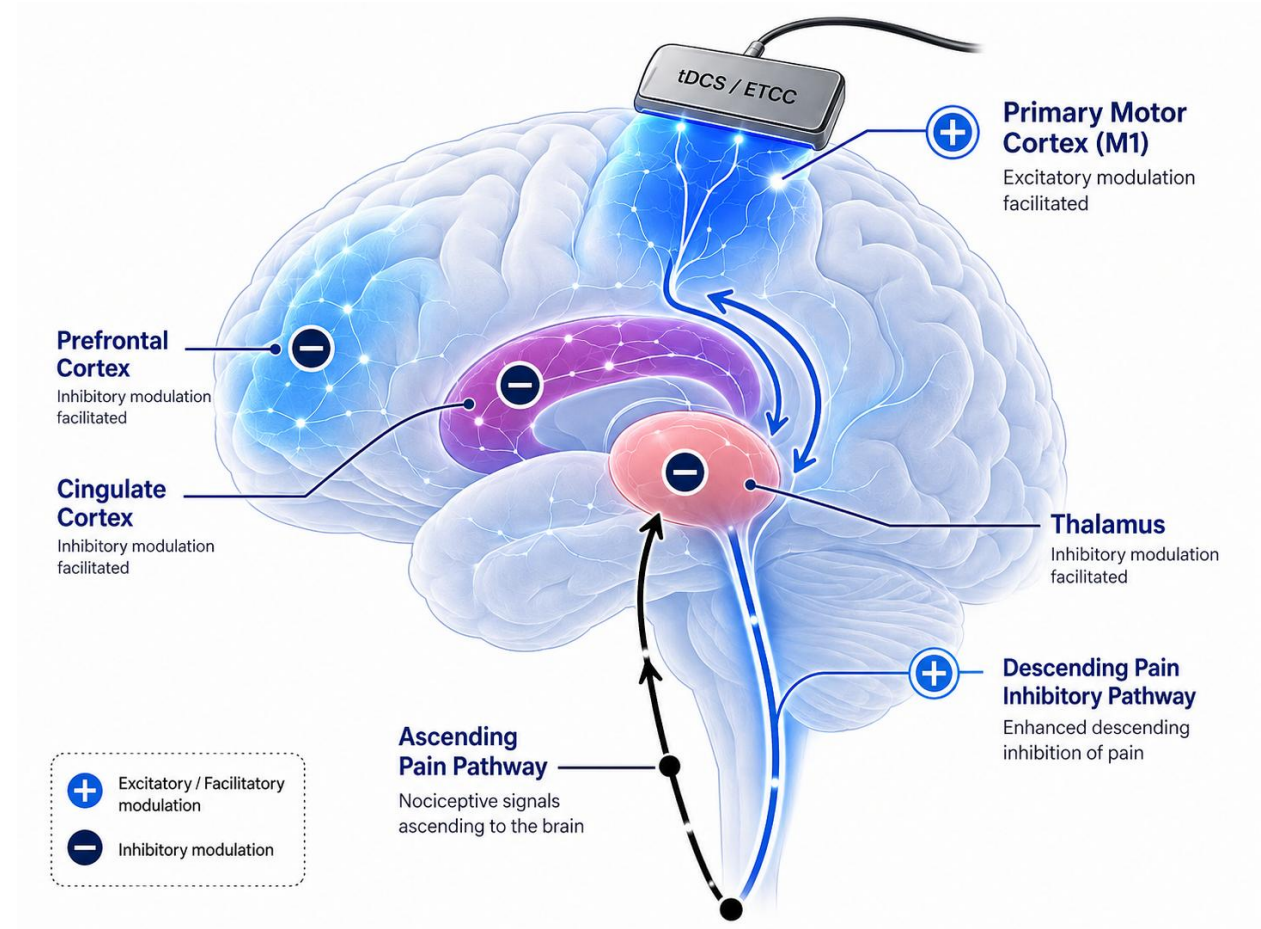
Lavrov, I., Latypov, T., Mukhametova, E. *et al.* Pre-motor versus motor cerebral cortex neuromodulation for chronic neuropathic pain. *Sci Rep* **11**, 12688 (2021).

ACC, anterior cingulate cortex; NAc, nucleus accumbens; Ins, insula.

DosSantos et al. Front Psychiatry. 2012.



Global Values: Baseline, 1.56; tDCS, 1.48
(4.5 % difference)



AI-generated illustration.



Pain-motor integration in chronic pain: A neurophysiological study

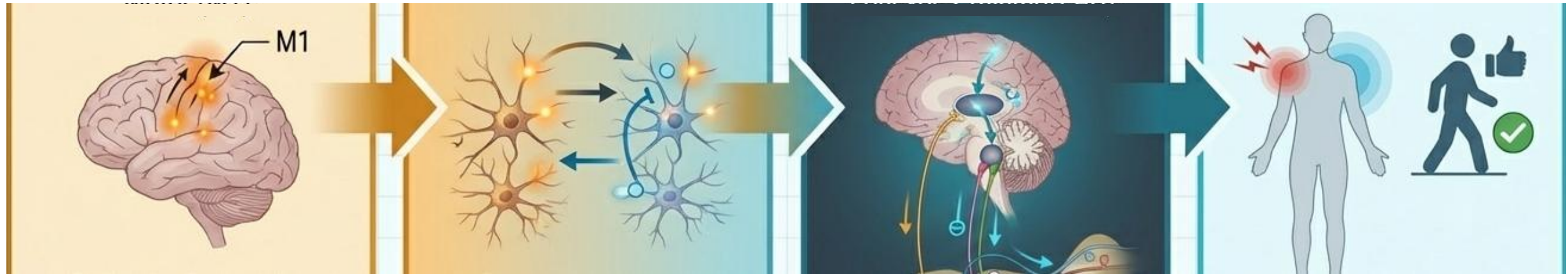
Francesco Asci ^{a b}✉, Giulia Di Stefano ^a ✉, Alessandro Di Santo ^c ✉,
Edoardo Bianchini ^d ✉, Caterina Leone ^a ✉, Silvia La Cesa ^e ✉, Alessandro Zampogna ^a ✉
, Giorgio Cruccu ^a ✉, Antonio Suppa ^{a b} ✉

People affected by chronic pain manifest M1 plasticity changes owing to abnormal pain-motor integration.

Level A

MEP, EEG, fMRI

Clinical results

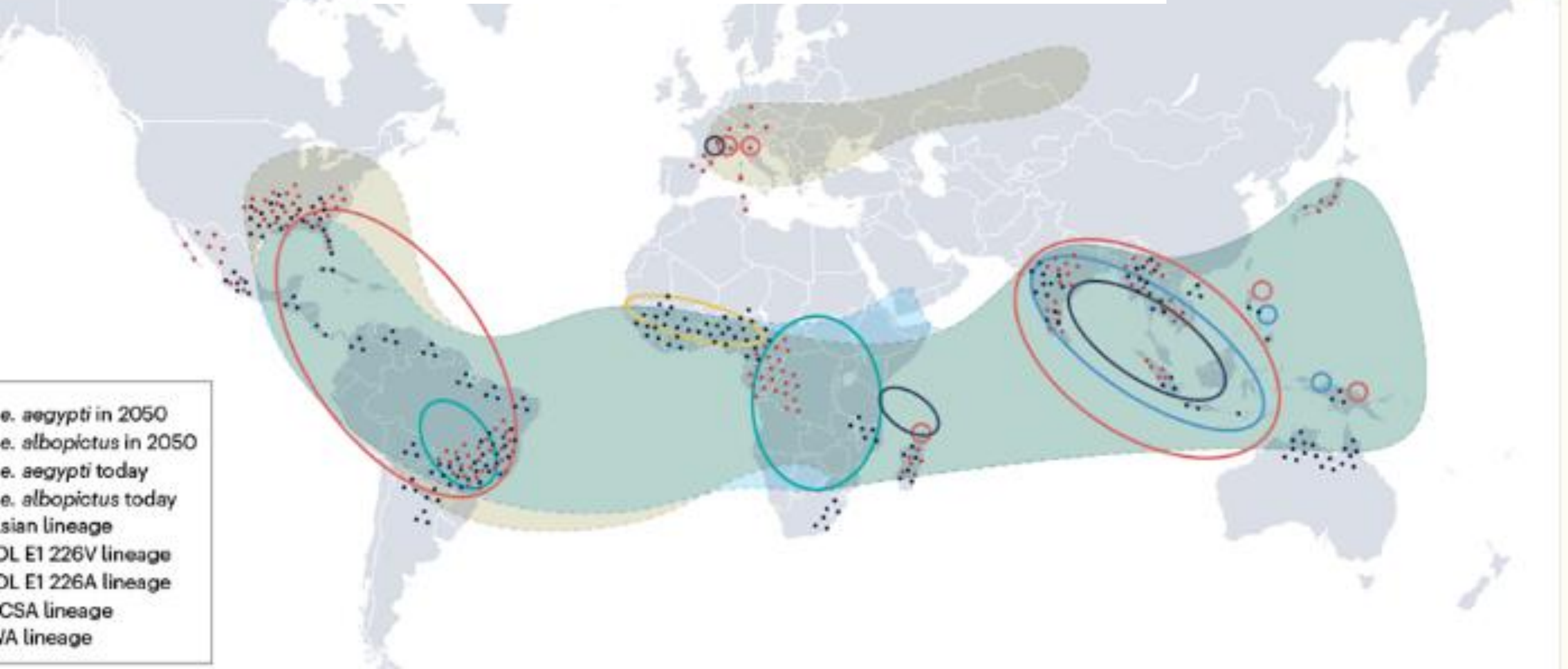




Studies Conducted by Our Research Group – NeuroClin

Chikungunya fever

[Koen Bartholomeeusen](#)¹, [Matthieu Daniel](#)^{2,3}, [Desiree A LaBeaud](#)⁴, [Philippe Gasque](#)^{2,5}, [Rosanna W Peeling](#)⁶,
[Kathryn E Stephenson](#)^{7,8}, [Lisa F P Ng](#)^{9,10,11}, [Kevin K Ariën](#)^{1,12}, [✉](#)

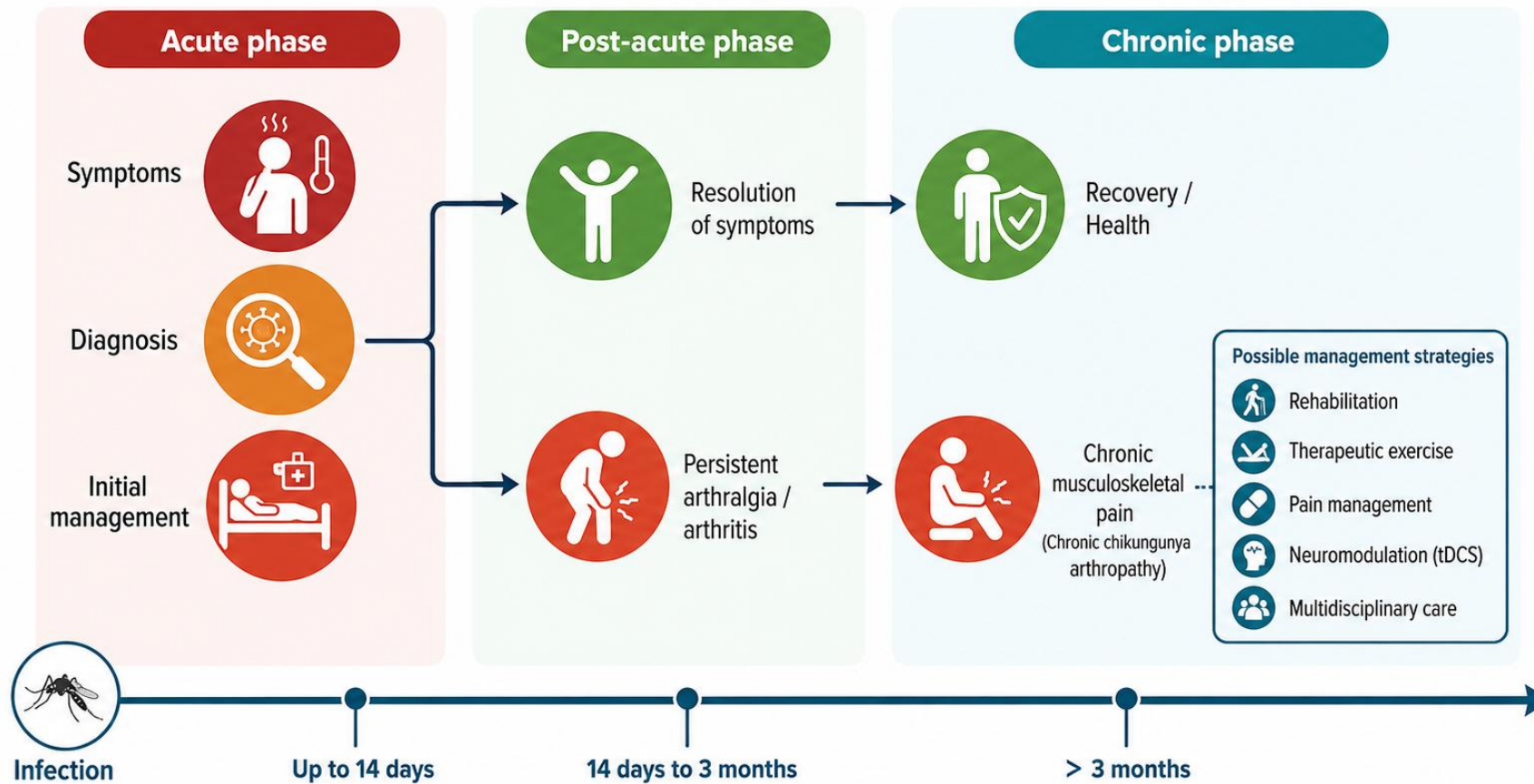




Looking for the future: Gaps in research and clinical rehabilitation for chronic chikungunya arthralgia

Rodrigo Pegado^{a,b,*} , Nilson N.Mendes Neto^{b,c}, Lucas Camargo^b, Kevin Pacheco-Barrios^{b,d}, Felipe Fregni^b

Clinical course of chikungunya



Chronic secondary musculoskeletal pain

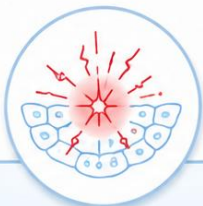
Nociceptive pain



Perpetuating
inflammation



Fatigue, arthralgias,
arthritis, myalgias,
and morning stiffness



1) Inflammation



2) Persistent
nociceptive input



3) Central
sensitization



4) Nociplastic pain

Perrot S, et al. *Pain*. 2019

Amaral JK, et al. *Viruses*. 2019

Chikungunya Arthralgia

SCIENTIFIC REPORTS

Scientific Reports

Neuromodulation treats Chikungunya arthralgia: a randomized controlled trial

🕒 2018 | Randomized controlled trial | Multicenter

BRAIN STIMULATION

Brain Stimulation

Alternate sessions of transcranial direct current stimulation (tDCS) reduce chronic pain in women affected by chikungunya: a randomized clinical trial

🕒 2020 | Randomized clinical trial | Multicenter

Annals of Physical and Rehab Medicine

Original article

Anodal tDCS over the motor cortex improves pain but not physical function in chronic chikungunya arthritis: randomized controlled trial

🕒 2020 | Randomized controlled trial | Multicenter



1

Endemic Context

15 randomized controlled trials (RCTs) are registered or under investigation, with strong Brazilian leadership in rehabilitation.



2

Core Protocol

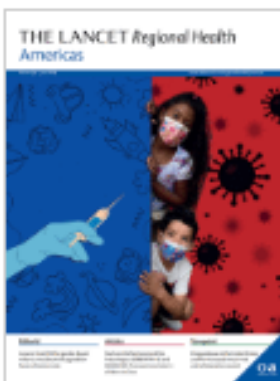
Anodal stimulation over the primary motor cortex (M1), delivered across 5 to 10 sessions.



3

Clinical Focus

Treatment of severe polyarticular inflammation transitioning to chronic nociplastic pain.



THE LANCET *Regional Health* Americas

Chikungunya crisis in the Americas: a comprehensive call for research and innovation

Rodrigo Pegado^{a,b,e} · Nilson N. Mendes Neto^{b,c,e} · Kevin Pacheco-Barrios^{b,d} · Felipe Fregni^b  

No studies on rehabilitation methods are available on clinicaltrials.gov and ReBEC lists **three recruiting** studies.

The symptomatic management was often combined with an **empirical** use of disease-modifying antirheumatic drugs and corticosteroids.

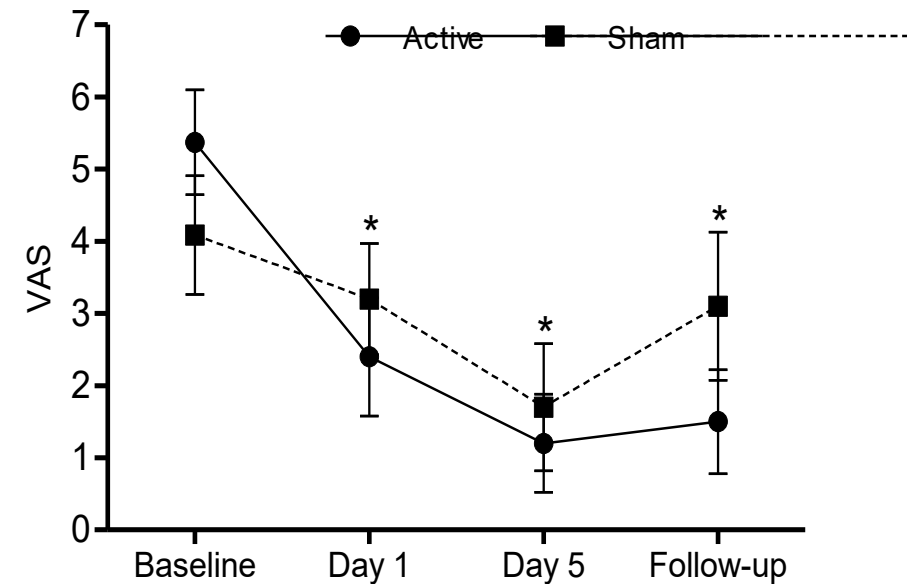
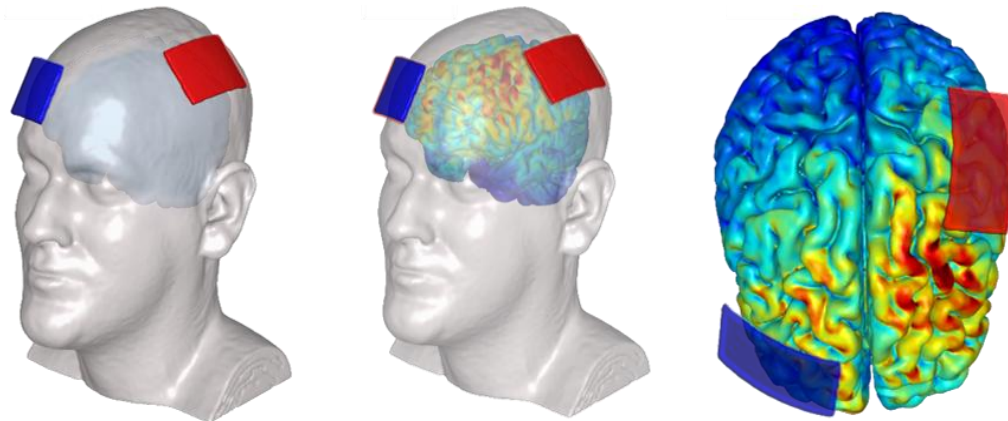
Chopra A et al. Best Pract Res Clin Rheumatol. 2025

► Sci Rep. 2018 Oct 30;8:16010. doi: [10.1038/s41598-018-34514-4](https://doi.org/10.1038/s41598-018-34514-4)

Neuromodulation treats Chikungunya arthralgia: a randomized controlled trial

[Edson Silva-Filho](#)¹, [Alexandre H Okano](#)², [Edgard Morya](#)³, [Jessica Albuquerque](#)⁴, [Enio Cacho](#)¹, [Gozde Unal](#)⁵,
[Marom Bikson](#)⁵, [Rodrigo Pegado](#)^{1,✉}

6258 Accesses | 37 Citations | 13 Altmetric |

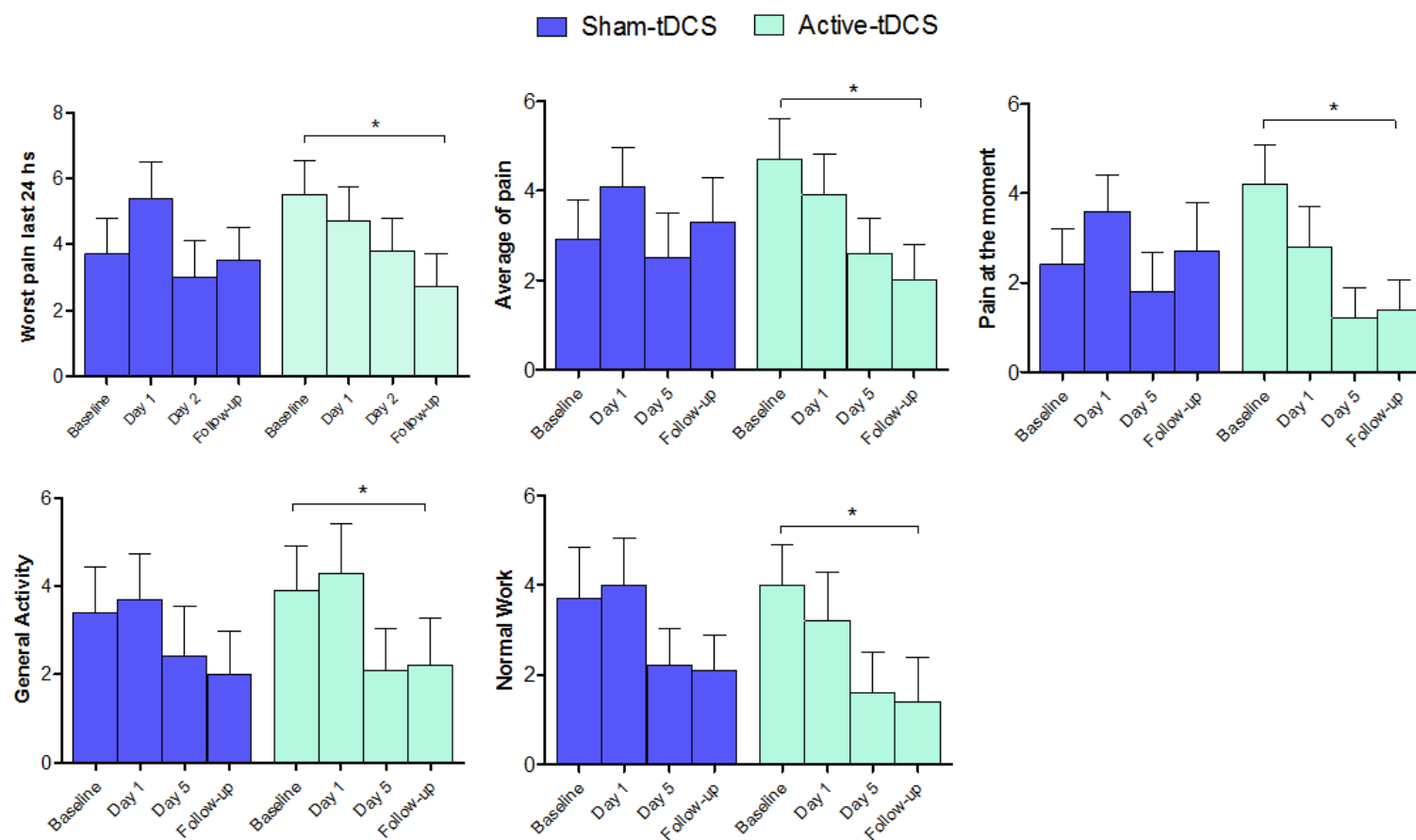


Neuromodulation treats Chikungunya arthralgia: a randomized controlled trial

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[Bikson](#) & [Rodrigo Pegado](#) ✉

6258 Accesses | 37 Citations | 13 Altmetric [Scientific Reports](#) 8, Article number: 16010 (2018)





Alternate sessions of transcranial direct current stimulation (tDCS) reduce chronic pain in women affected by chikungunya. A randomized clinical trial

Clecio Gabriel De Souza ^{a, b, 1, *}, Rodrigo Pegado ^{a, h, 1}, Jardson Costa ^c, Edgard Morya ^{d, g, h, 1},
Abrahão Fontes Baptista ^{e, g, h}, Gozde Unal ^f, Marom Bikson ^f, Alexandre Hideki Okano ^{e, g, h}

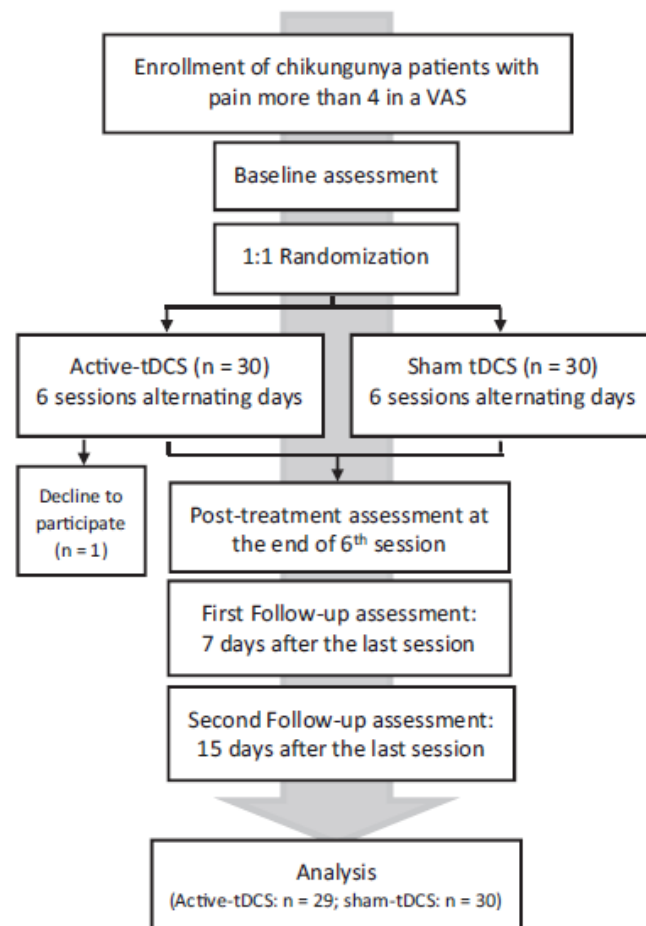
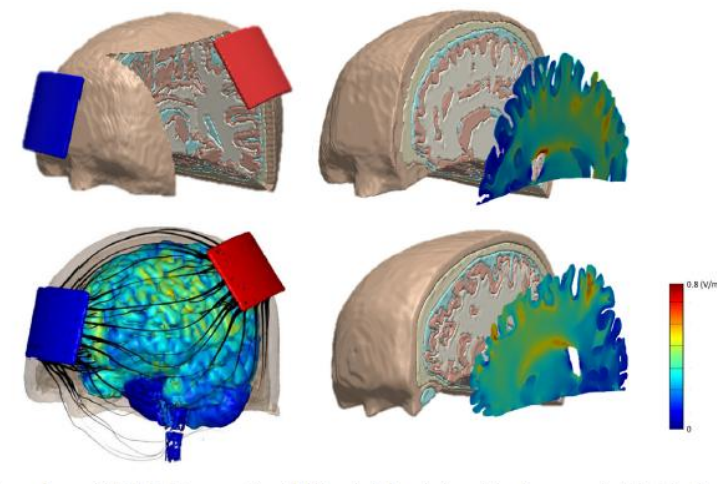


Fig. 1. Flowchart of the progress through the phases of randomized double-blinded clinical trial of two groups.



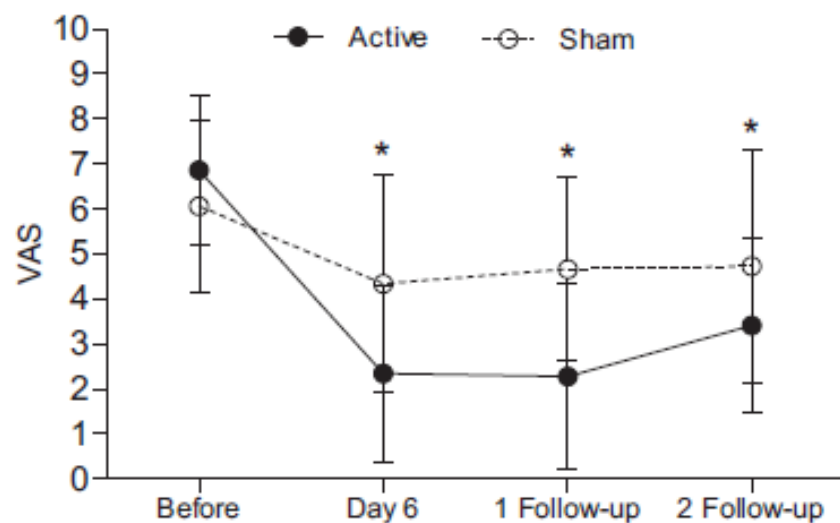
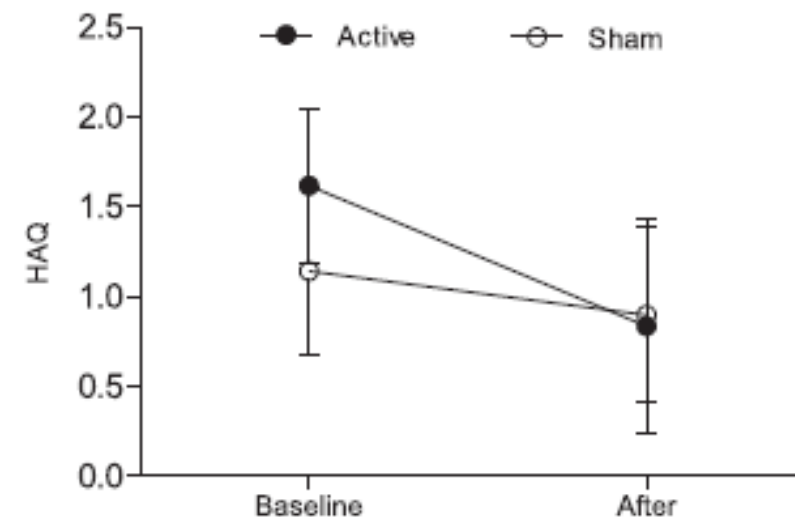


Fig. 3. Pain reduction was observed in short and long-term only in active-tDCS (n = 29) when compared with sham-Group (n = 30). Mixed ANOVA showed a significant interaction between the group and time ($p < 0.0001$) with a group effect ($p < 0.05$) over time. *Significant difference between groups in day 6 ($p = 0.001$; mean difference: 1.98), 1st (7 days after last tDCS session) follow-up ($p = 0.0001$; mean difference: 2.39) and 2nd (15 days after last tDCS session) follow-up ($p = 0.0001$; mean difference: 1.32) Pairwise comparisons with Bonferroni adjustment.



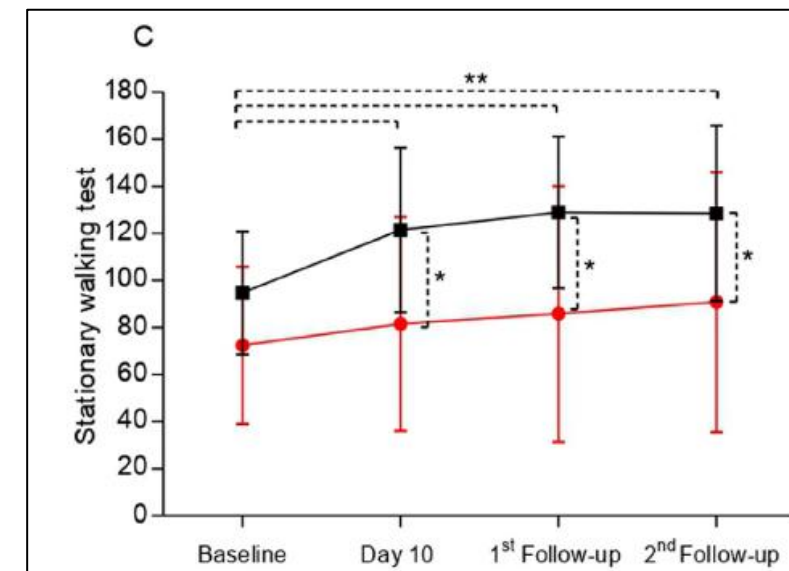
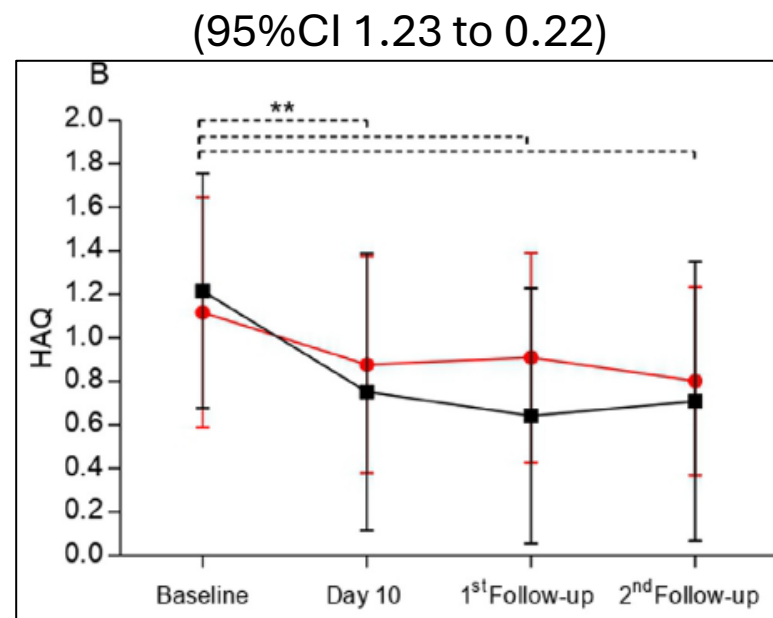
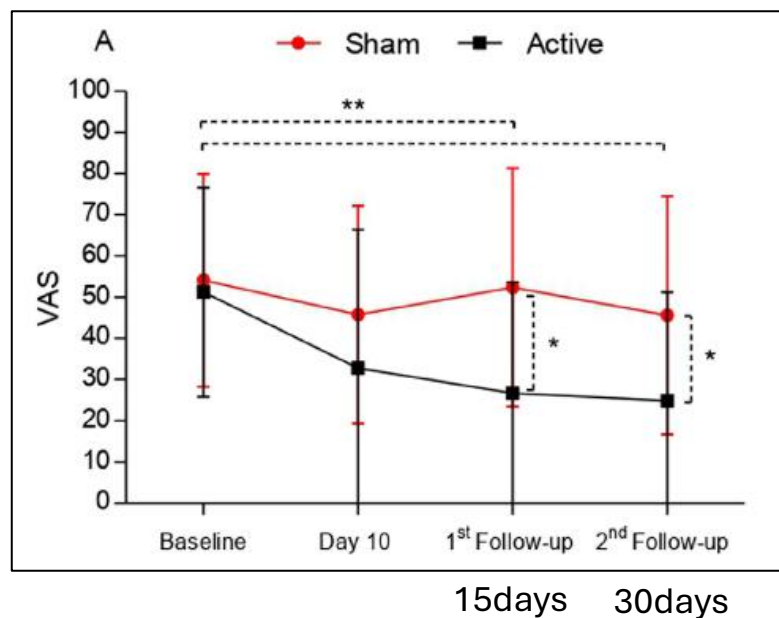
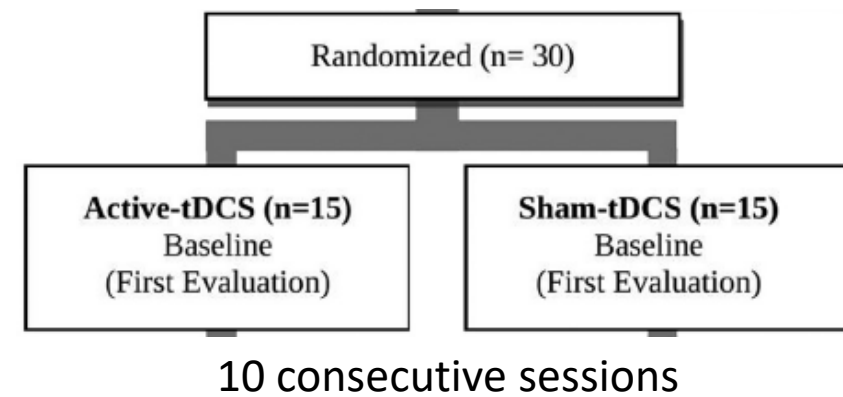
Significant interaction between the group and time on HAQ.



Original article

Anodal tDCS over the motor cortex improves pain but not physical function in chronic chikungunya arthritis: Randomized controlled trial

Antônio Felipe Lopes Cavalcante^a, Joanna Sacha Cunha Brito Holanda^b, João Octávio Sales Passos^a, Joyce Maria Pereira de Oliveira^b, Edgard Morya^c, Alexandre H. Okano^d, Marom Bikson^e, Rodrigo Pegado^{a,b,*}



Chronic Pain in End-Stage Kidney Disease (ESKD)



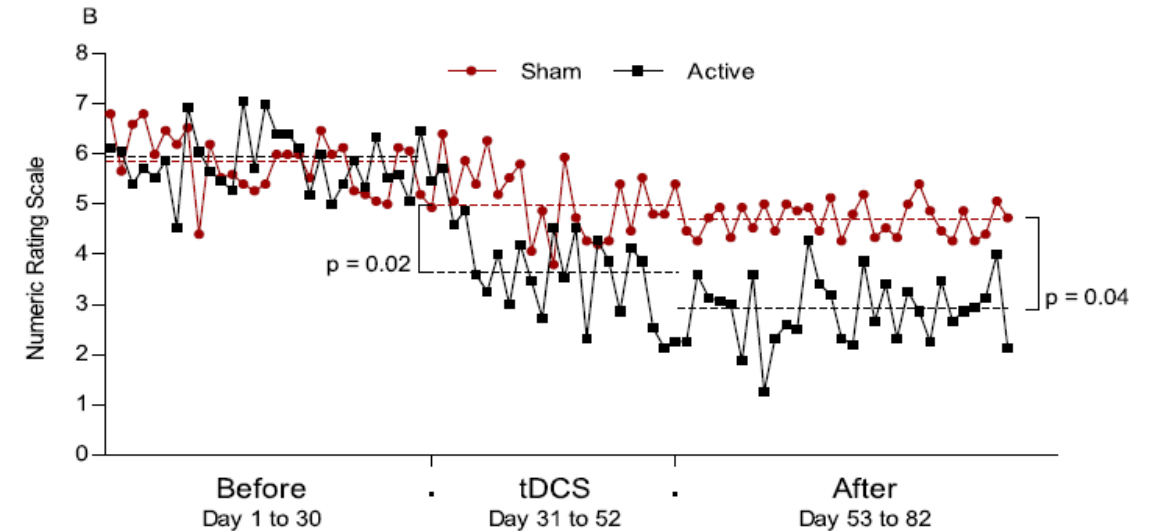
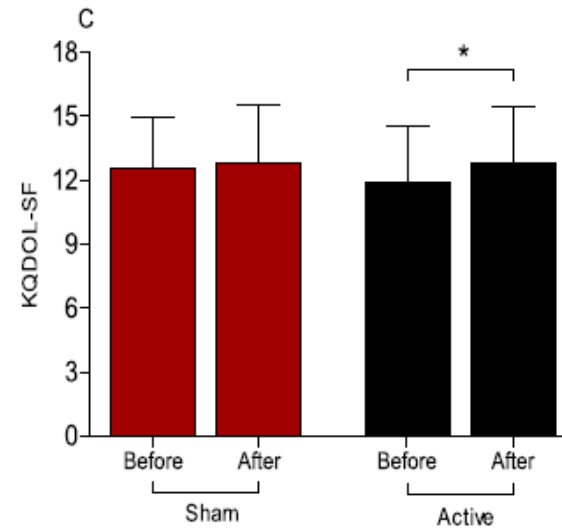
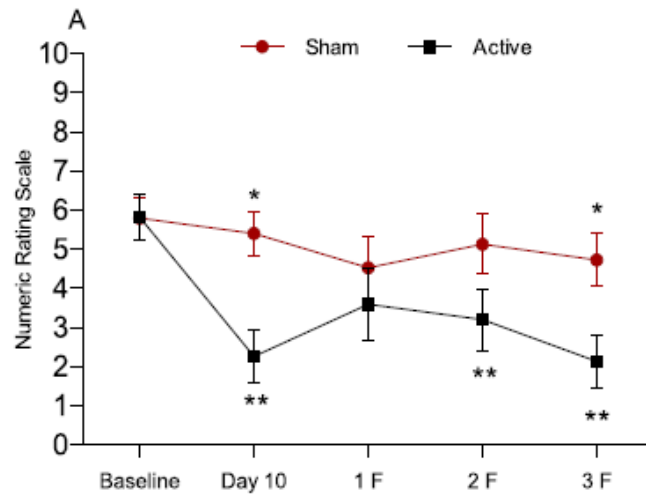
Transcranial Direct Current Stimulation (tDCS): Pain Management in End-Stage Renal Disease - Report of an Early Randomized Controlled Trial

Check for updates

Artur Quintiliano, MD, PhD, Marom Bikson, PhD, Tayanne Oehmen, RN, Rodrigo Pegado, PT, PhD, and Gianna Mastroianni Kirsztajn, MD, PhD

234 *Journal of Pain and Symptom Management*

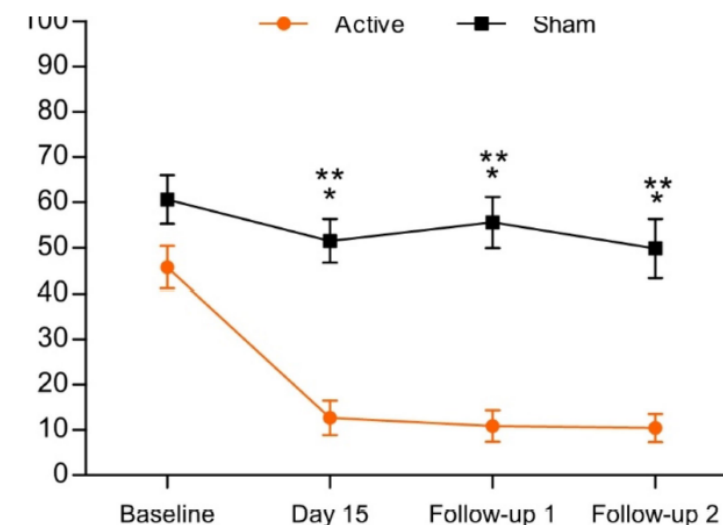
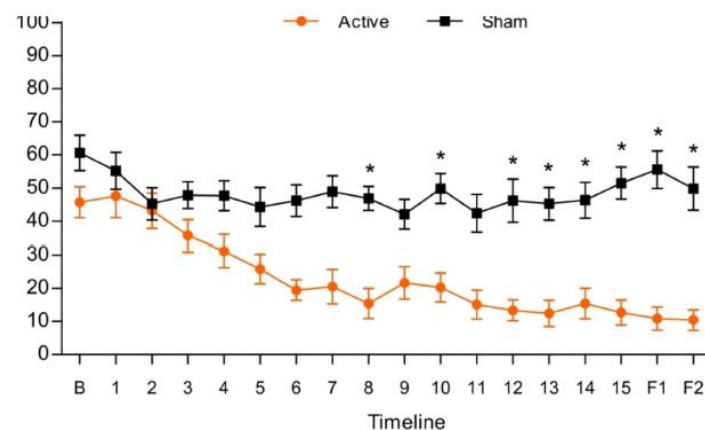
Vol. 64 No. 3 September 2022

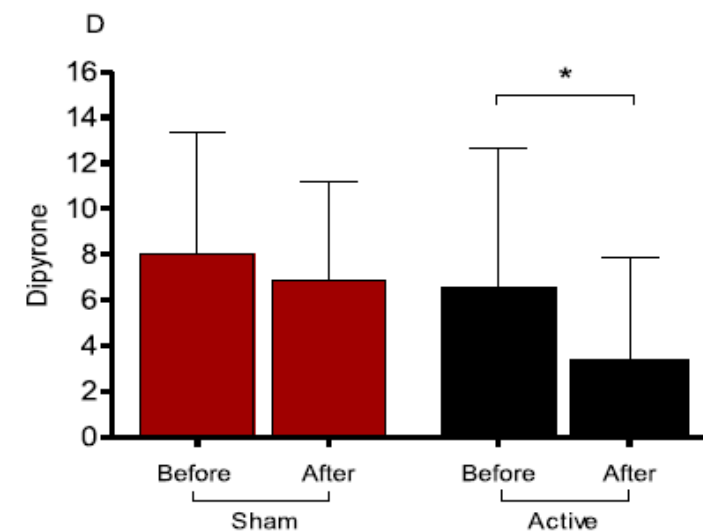
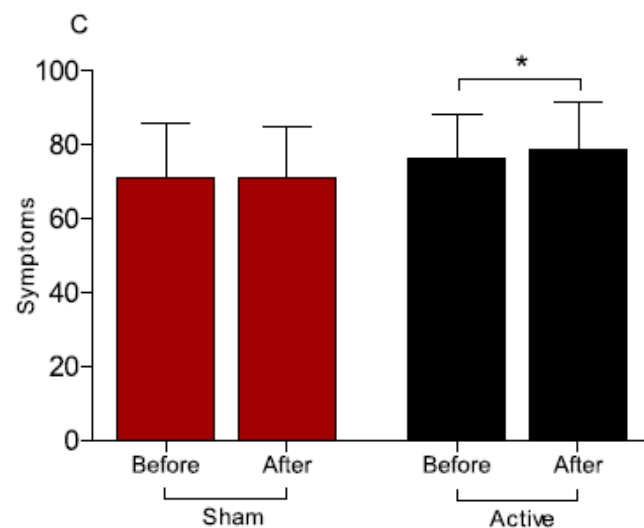
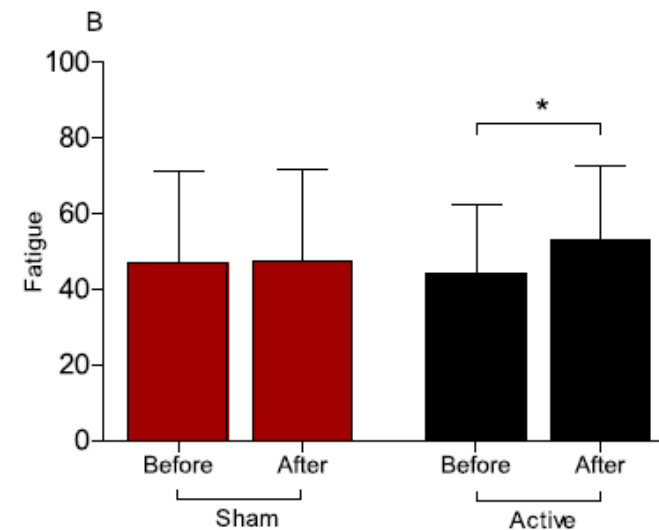
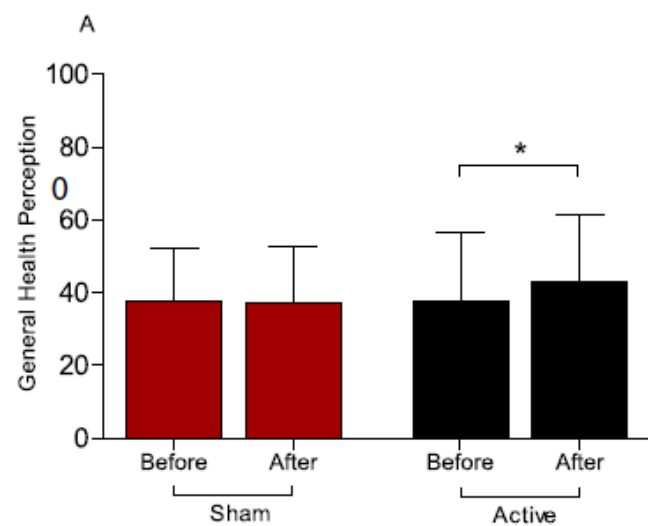


Transcranial direct current stimulation over motor cortex improves pain in end stage renal disease a randomized controlled trial

Eduarda Fonseca Mendes¹, Edson Silva-Filho¹, Joanna Brito Holanda², M. G. L. Matias², Tatiana Camila Lima¹, Sara Costa², Artur Quintiliano^{3,4}, Kevin Pacheco-Barrios^{5,6}, Felipe Fregni⁵ & Rodrigo Pegado^{4,2,5}

Scientific Reports | (2025) 15:21943





Primary Dysmenorrhea





ORIGINAL RESEARCH

Changes of functional connectivity of the anterior cingulate cortex in women with primary dysmenorrhea

Peng Liu^{1,2} • Yanfei Liu^{1,2} • Geliang Wang^{1,2} • Ru Li^{1,2} • Ying Wei^{1,2} • Yingying Fan^{1,2} • Yang Yu^{1,2} • Demao Deng³ • Wei Qin^{1,2}

SCIENTIFIC REPORTS

OPEN

Dynamic Changes of Functional Pain Connectome in Women with Primary Dysmenorrhea

Received: 04 December 2015
Accepted: 31 March 2016
Published: 19 April 2016

Ting-Hsuan Wu^{1,2,*}, Cheng-Hao Tu^{1,2,*}, Hsiang-Tai Chao^{3,4}, Wei-Chi Li¹, Intan Low⁵, Chih-Ying Chuang², Tzu-Chen Yeh^{1,2}, Chou-Ming Cheng², Chih-Che Chou², Li-Fen Chen^{1,2,5} & Jen-Chuen Hsieh^{1,2}



Effects of Transcranial Direct Current Stimulation for Treatment of Primary Dysmenorrhea: Preliminary Results of a Randomized Sham-Controlled Trial

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OXFORD
ACADEMIC

Pain Medicine

Rodrigo Pegado, PhD ✉, Luana Karyne Silva, Ugrad Res,
Hégila da Silva Dantas, Ugrad Res, Hialison Andrade Câmara, Ugrad Res,
Karime Andrade Mescouto, PT, Edson Meneses Silva-Filho, PT,
Johnnatas Mikael Lopes, PhD, Maria Thereza Albuquerque Barbosa Cabral Micussi, PhD,
Grasiéla Nascimento Correia, PhD

Pain Medicine, Volume 21, Issue 12, December 2020, Pages 3615–3623,

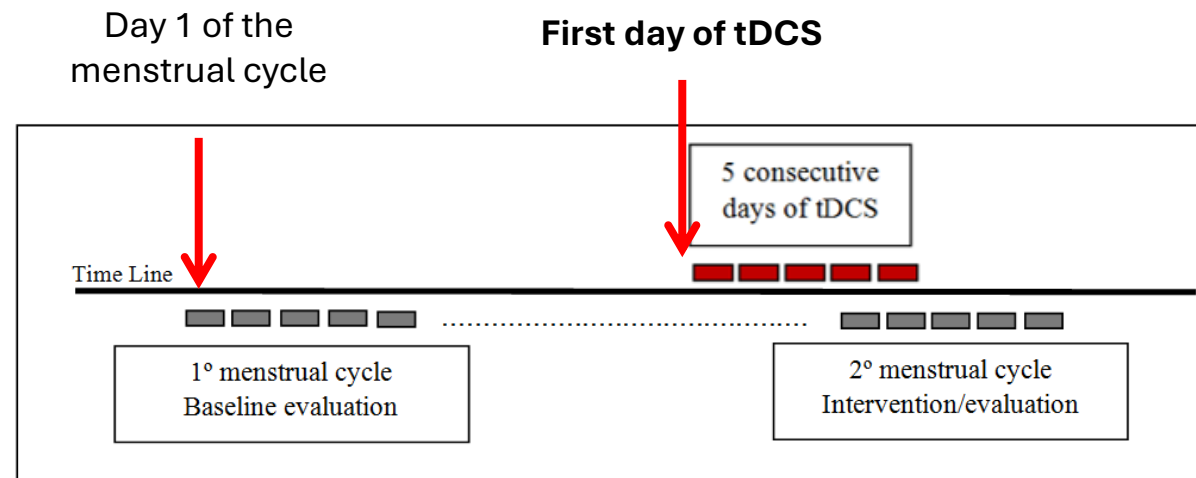


Figure 2. Methodology of intervention. Subjects received intervention with tDCS (active or Sham) during the second menstrual cycle for five consecutive days.

In the second menstrual cycle...

Active-tDCS produced a huge reduction in NRS scores in post-1st (means 7.81 vs 5.18; $p < .001$; $d = 1.55$), a large reduction in post-2nd (5.81 vs 4.36; $p = .025$; $d = 0.70$), and post-3rd (4.09 vs 2.45; $p = .019$; $d = 0.72$)

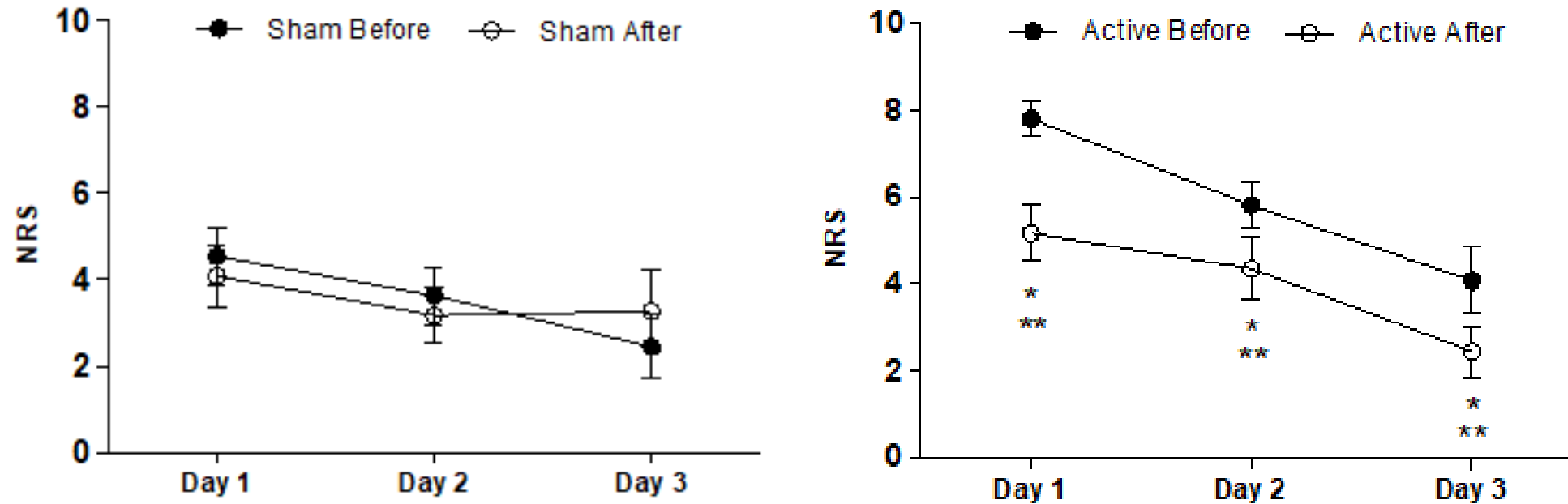
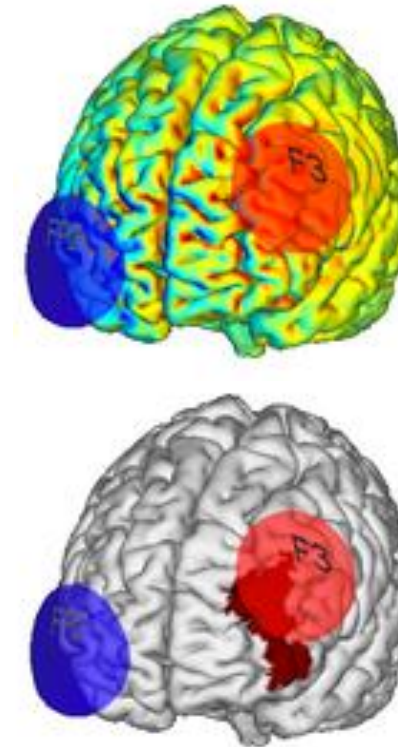
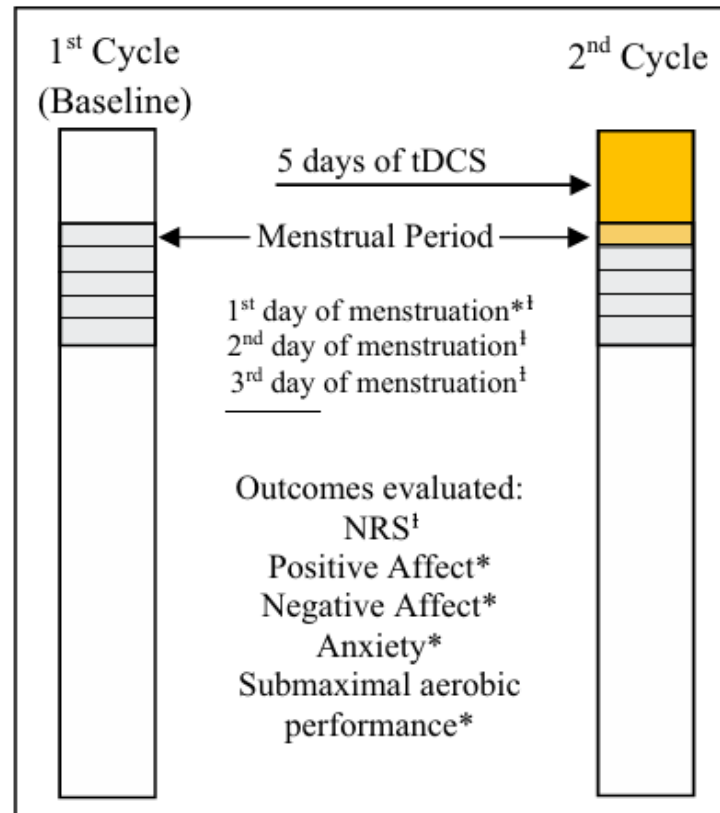


Figure 3. Changes in VAS pain scores over time by treatment group: group $\times$ time interaction from pre- to post-intervention. (Wald $\chi^2 = 8.19$; $p = .004$).

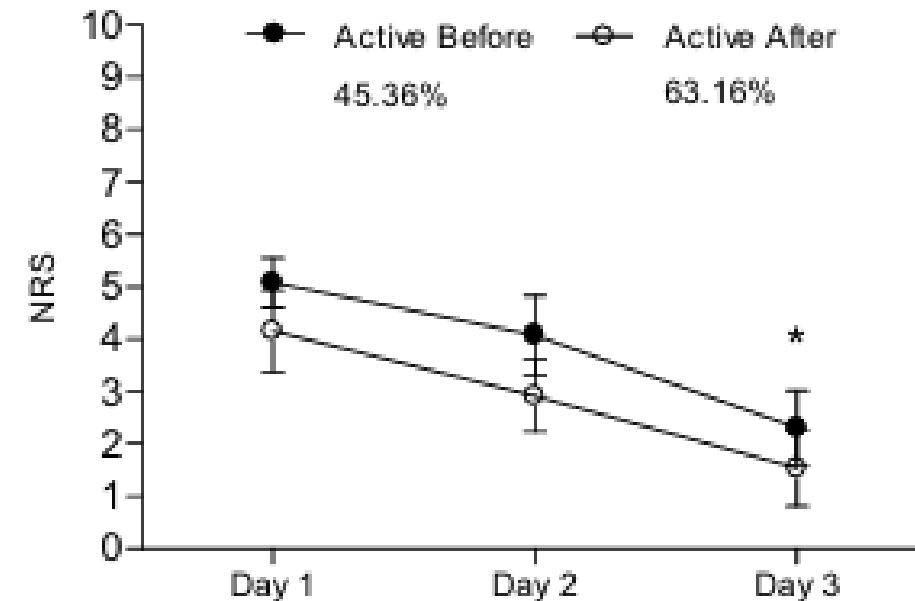
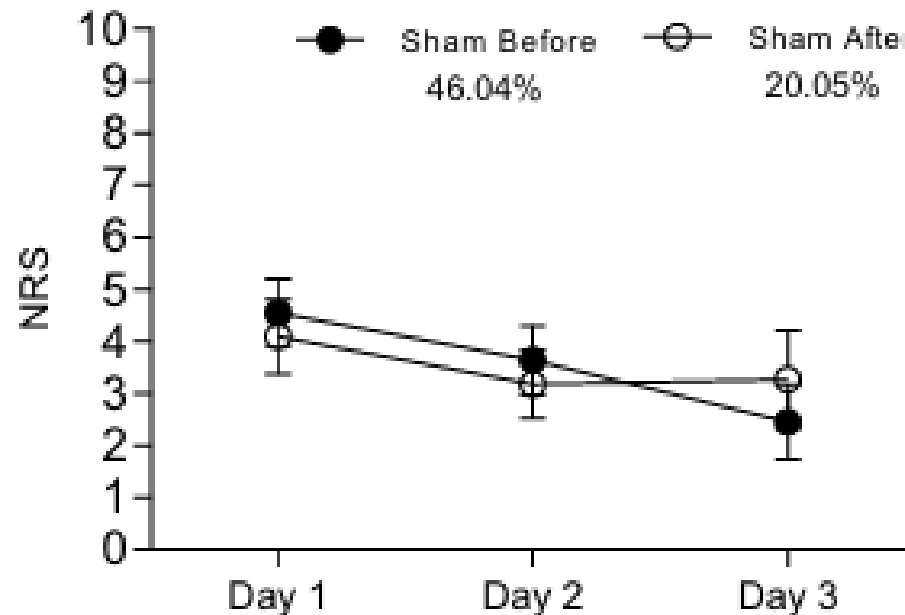
Modulating Anxiety and Functional Capacity with Anodal tDCS Over the Left Dorsolateral Prefrontal Cortex in Primary Dysmenorrhea

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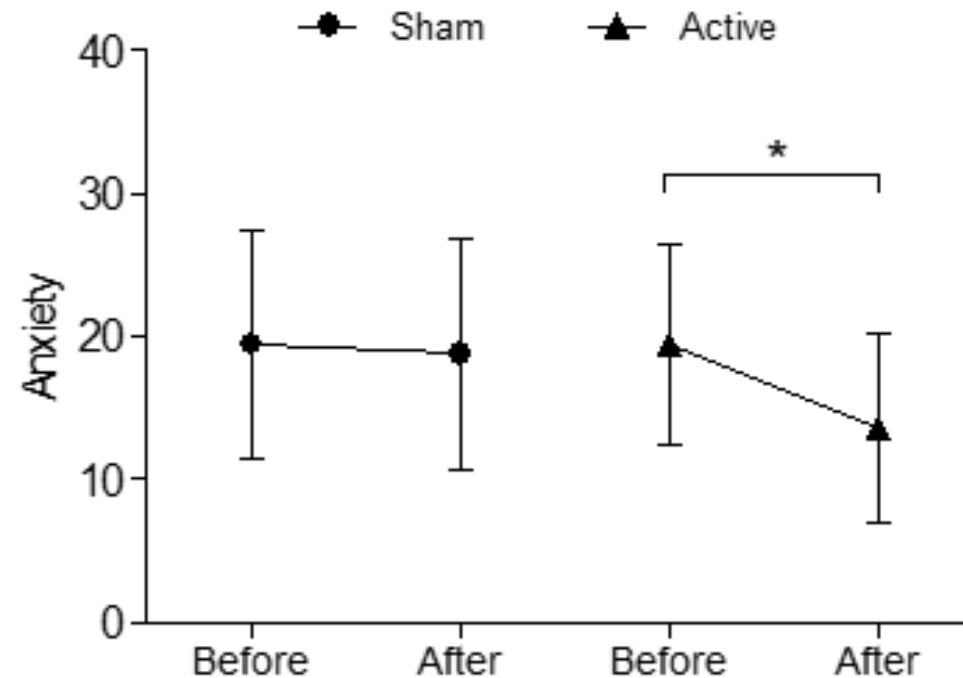
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[F(2,44) = 1.358, p = 0.26]

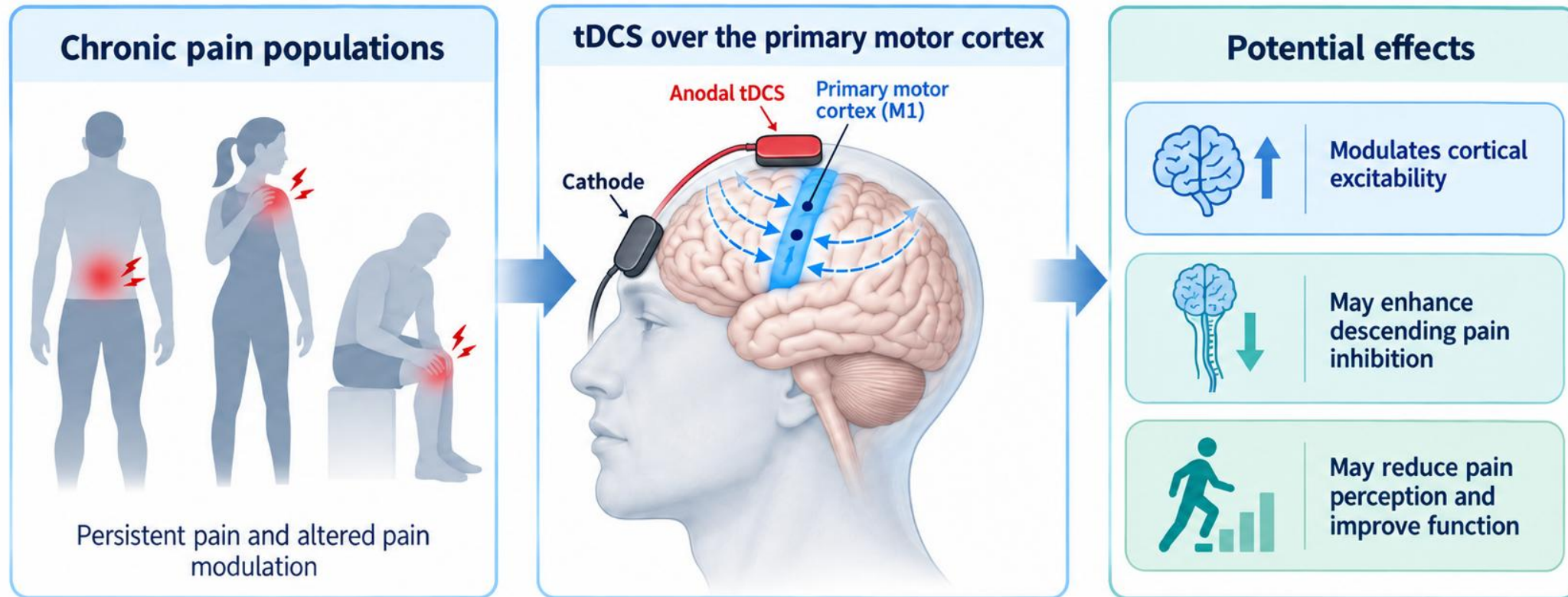
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tDCS over the Primary Motor Cortex in Chronic Pain

A simplified overview



Takeaway: M1 tDCS is used as a neuromodulation strategy to help modulate pain processing in chronic pain populations.

Rodrigo Pegado

Associate Professor
Department of Physical Therapy
Graduate Program in Health Science
Graduate Program in Physical Therapy
Federal University of Rio Grande do Norte - Brazil
Principal Investigator - Clinical Neuromodulation Group
(NeuroClin)



rodrigo.pegado@ufrn.br

Funding and supporting agencies



Our Academic Home and Research Group

