Transcranial direct current stimulation: A promising tool to help understand and enhance gait and balance in older adults

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- NIH / NIA
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- U.S.-Israel Binational Science Foundation
- Marcus Applebaum Research Award
- Harvard Football Players Health Study
- Neuroelectrics, Inc.

Higher-level control of gait and balance in older adults

Transcranial current stimulation (tCS) – quick overview

tDCS holds promise to improve gait and balance in older adults

Limitations / needs for future research: Optimal targets; Personalization; Accessibility

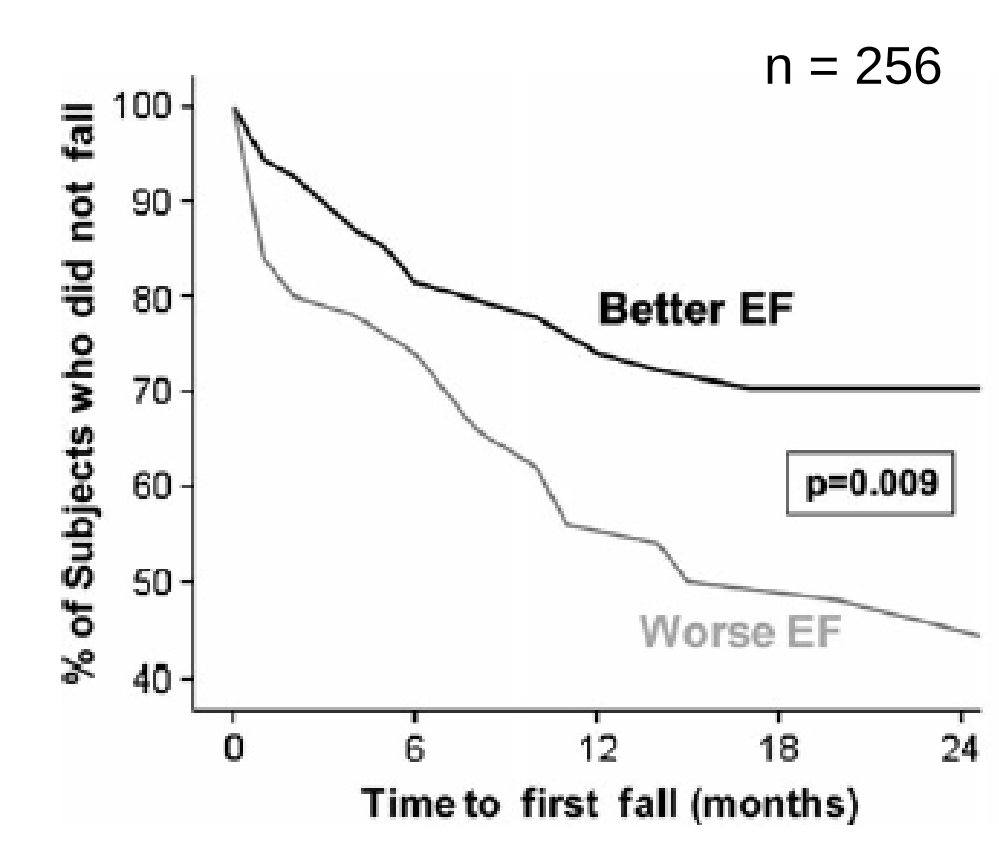
Aging is associated with progressive decline in mobility and cognitive function.

1 in 3 older adults will suffer from
Alzheimer's disease or related dementia.

1 in 3 older adults fall
each year.

Are they separate issues?

Mobility and cognition are intertwined.

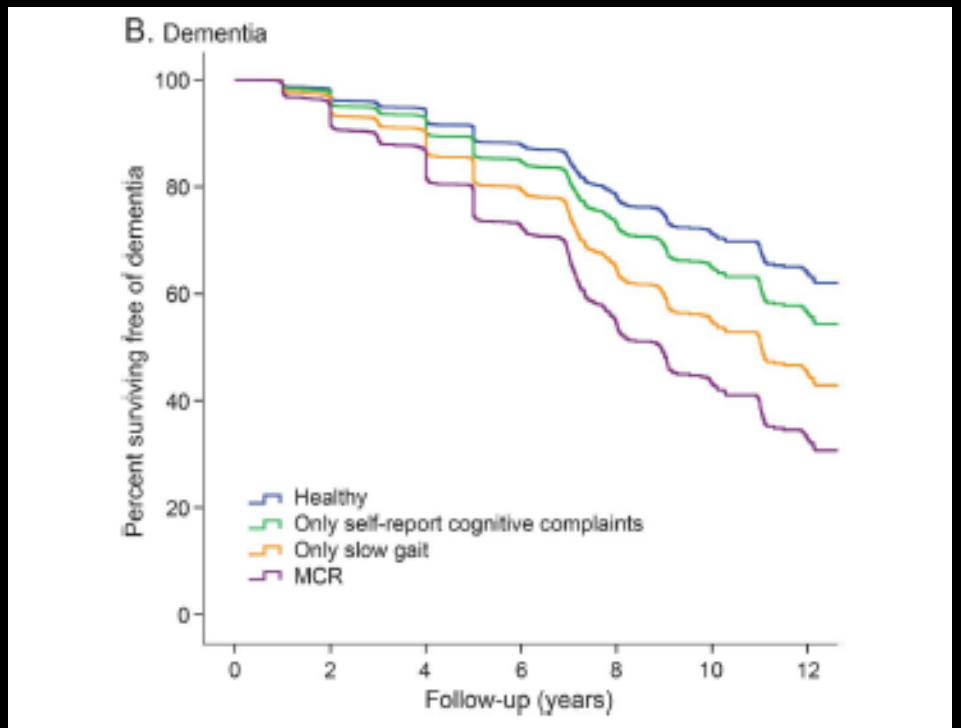


- Lowest quartile = 3x more likely to suffer a fall
- Highest quartile = Less likely to fall than all others

Herman et al, J Gerontol, 2010

Mobility and cognition are intertwined.

n = 26,000



Kaplan-Meier survival curves with 95% confidence interval over 12 years' follow-up in pooled samples. MCR = motoric cognitive risk syndrome.

After adjusting for age, sex, education and cohort source:

- Cognitive complaints alone:
  - 9% more likely
- Slow gait alone:
  - 40% more likely
- Both:
  - 72% more likely

Verghese et al, Neurology, 2014

Why are mobility and cognitive outcomes intertwined?

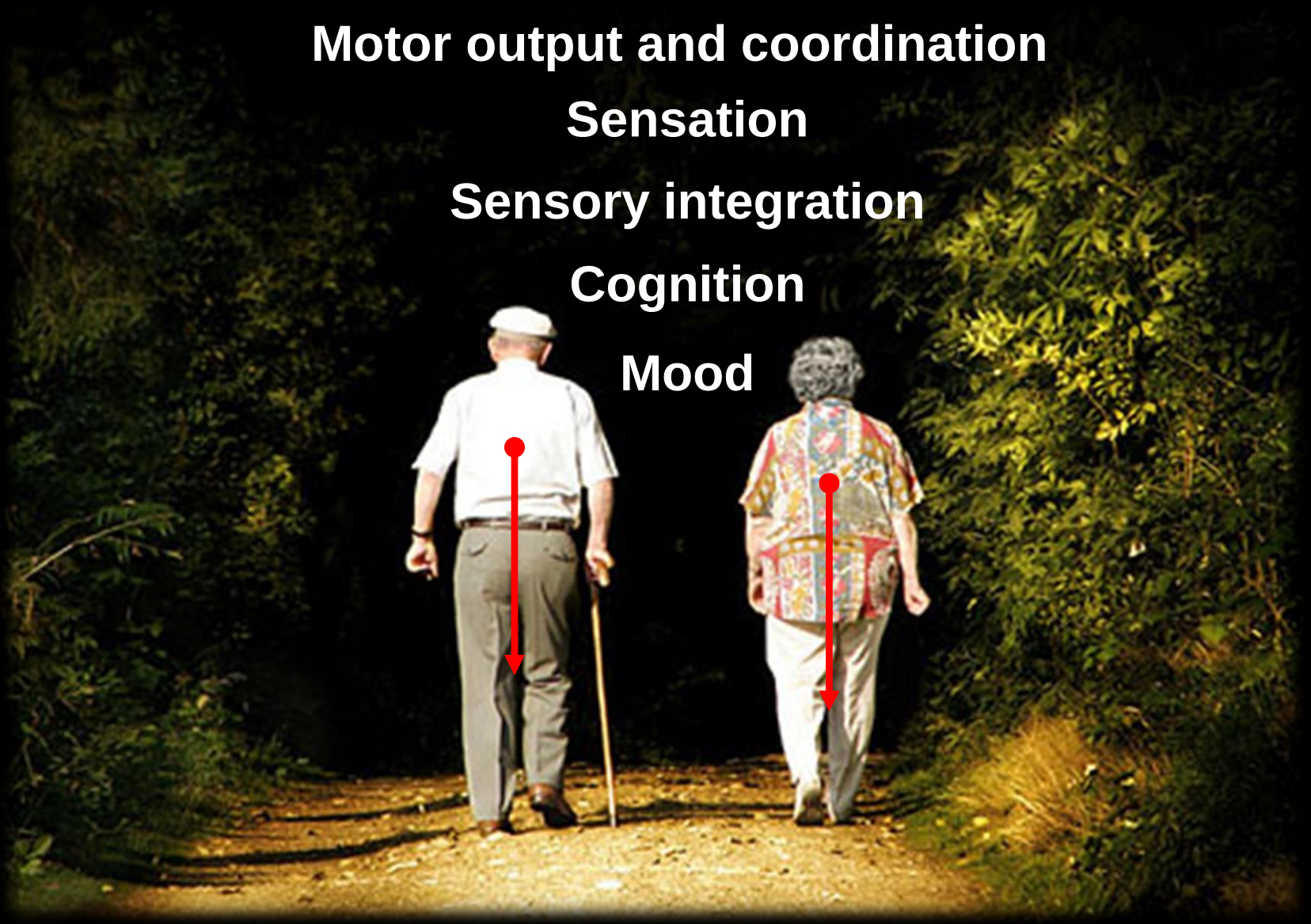
Motor output and coordination

Sensation

Sensory integration

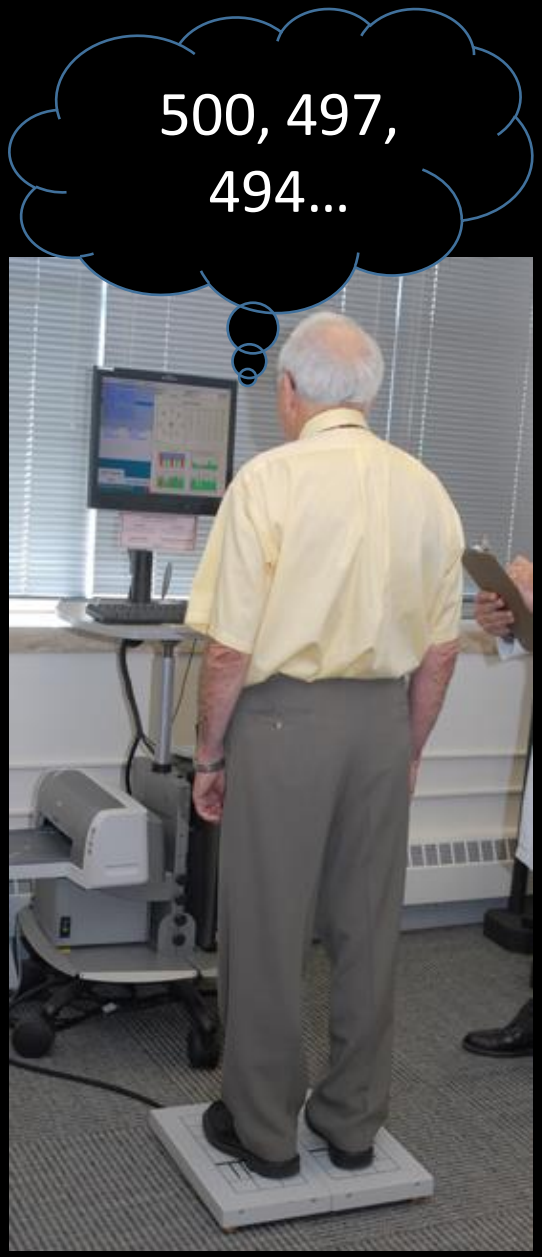
Cognition

Mood

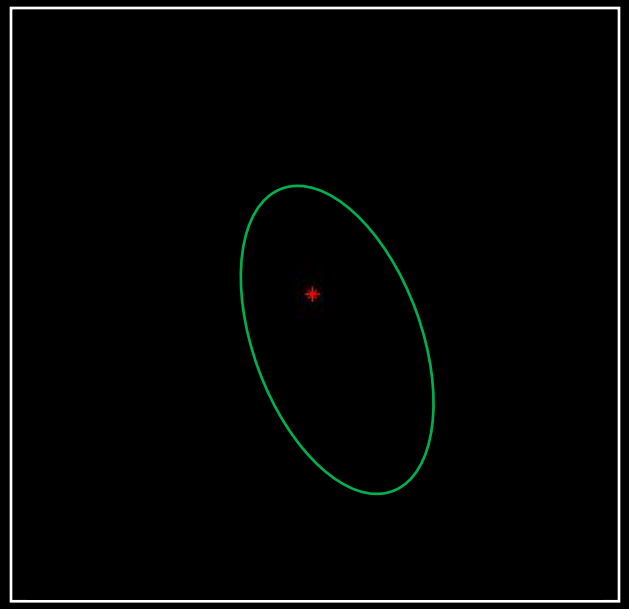


It’s even more complicated…

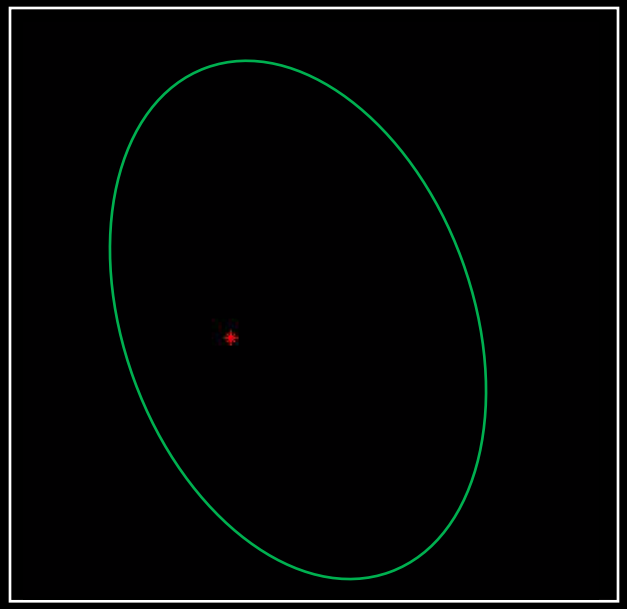
Cognitive dual tasking
is the norm…
and it disrupts our balance!

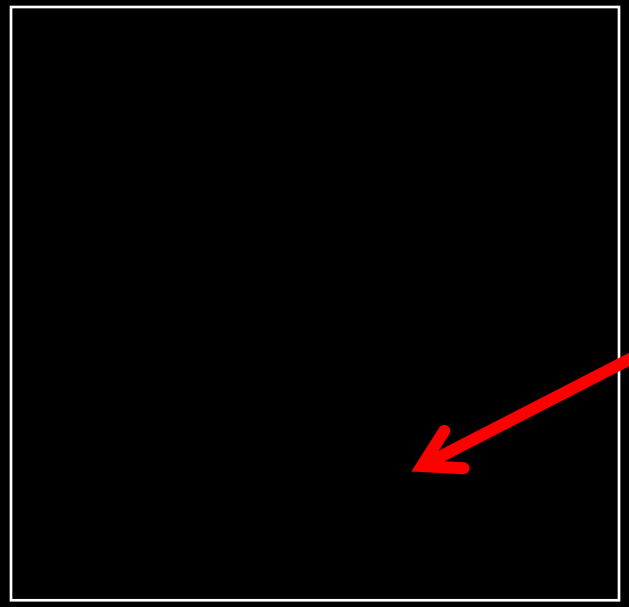


Standing



Standing + Counting





Dual task "cost"

We can also measure the dual task cost to walking.

Walking

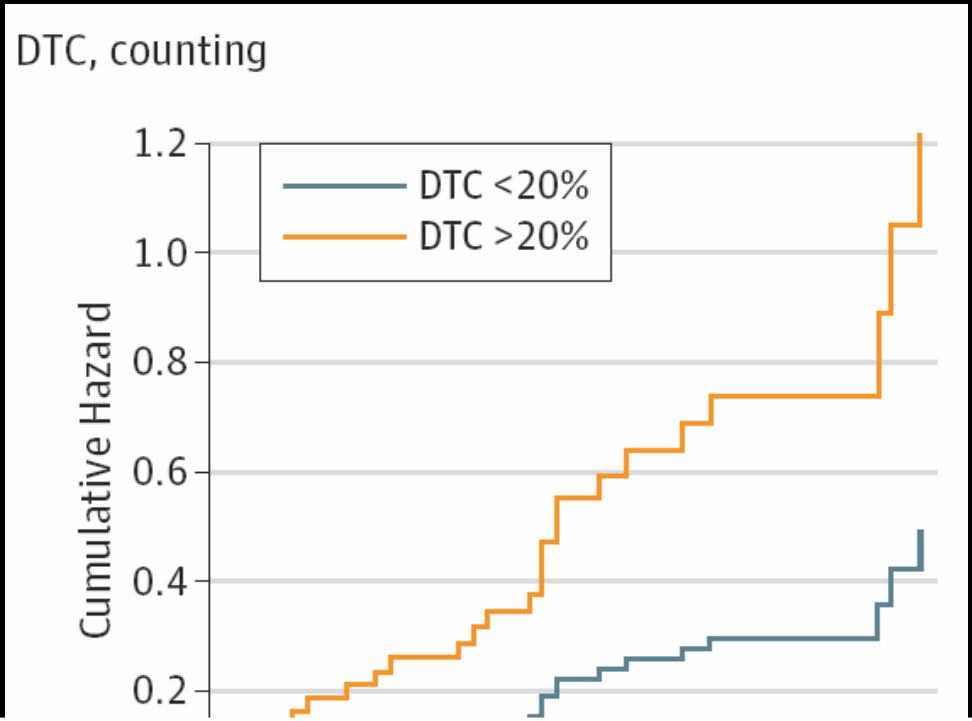
Walking + Counting

If you are over the age of 65 and free of overt disease, yet your dual task cost to gait speed is >18%, you are 3 times more likely to fall in the next 5 years.

Hausdorff et al, J of Gerontology, 2016

Dual task performance predicts future falls. …and cognitive decline

n = 112; 6 year follow-up; HR = 3.79

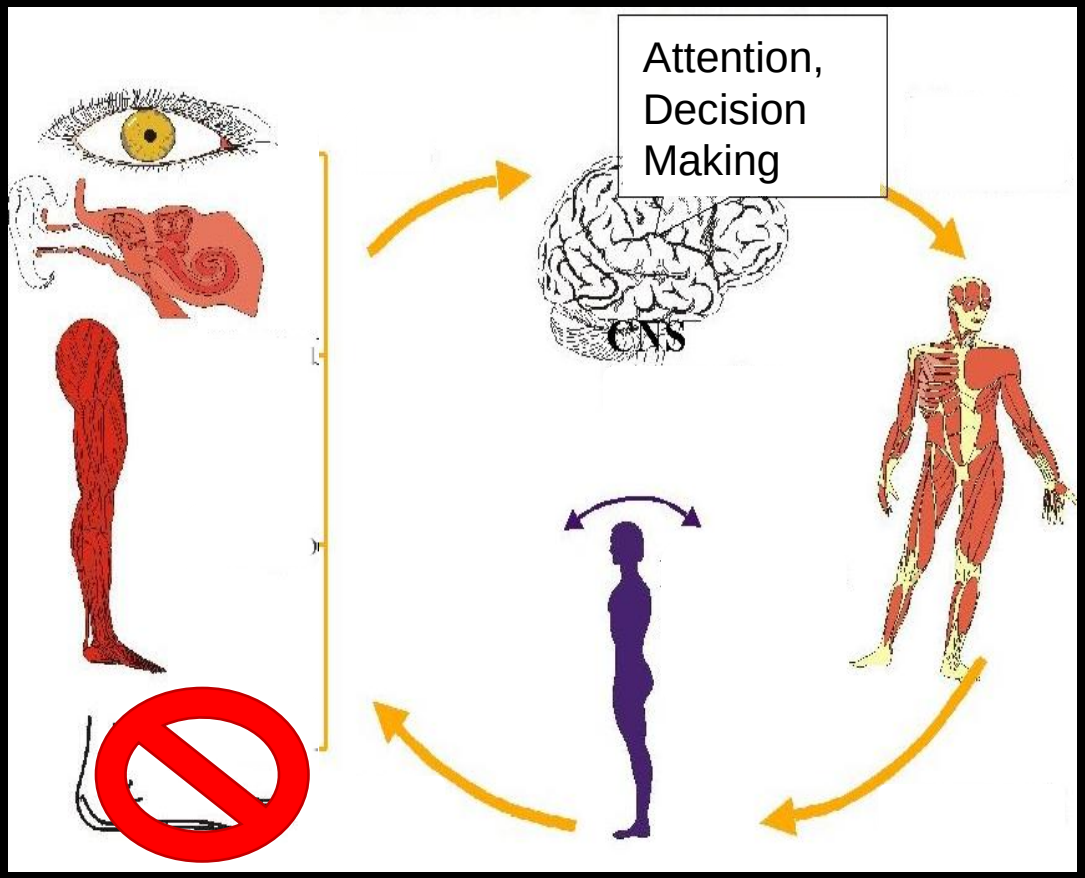


"Dual-task gait was comparable with cognitive testing to predict incident dementia, and adjustments for baseline cognition only partially attenuated associations when modeled as a dichotomous variable, suggesting that dual-task gait provides extra information not captured by cognitive testing."

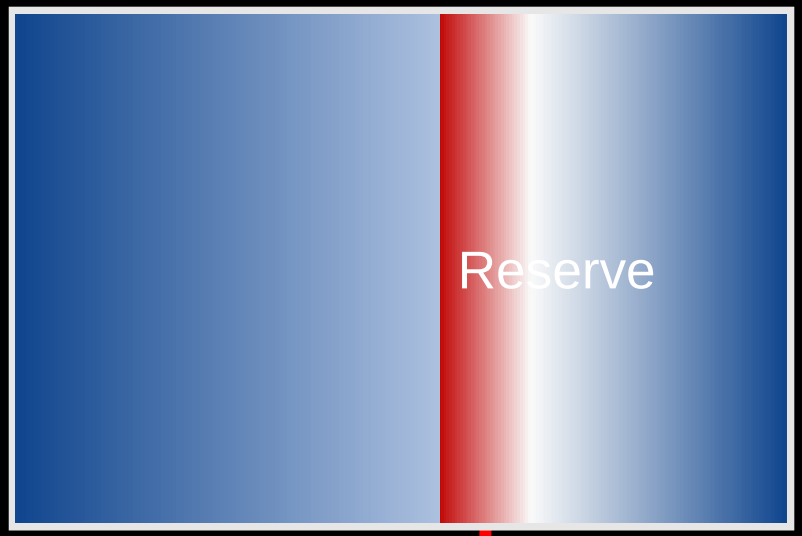
Montero-Odasso et al, JAMA Neurology, 2017

Why does dual task cost occur?

Balance control system



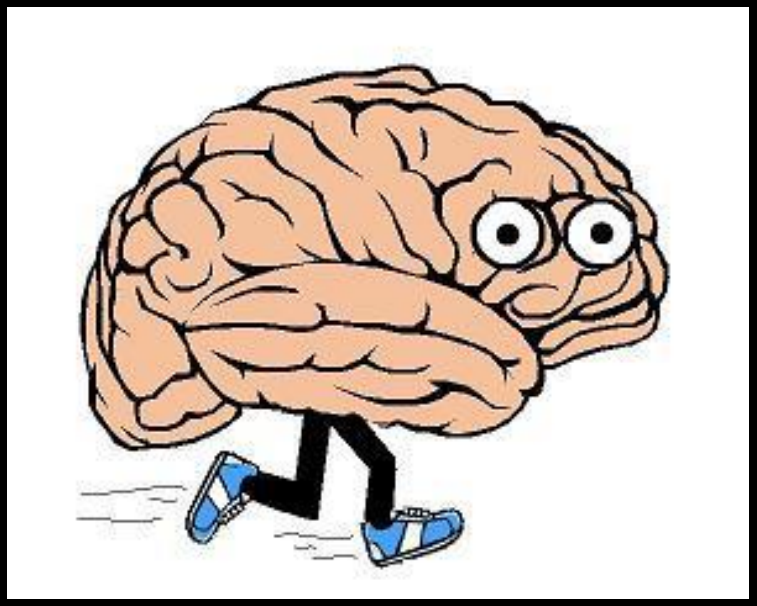
Cognitive Resources



Standing

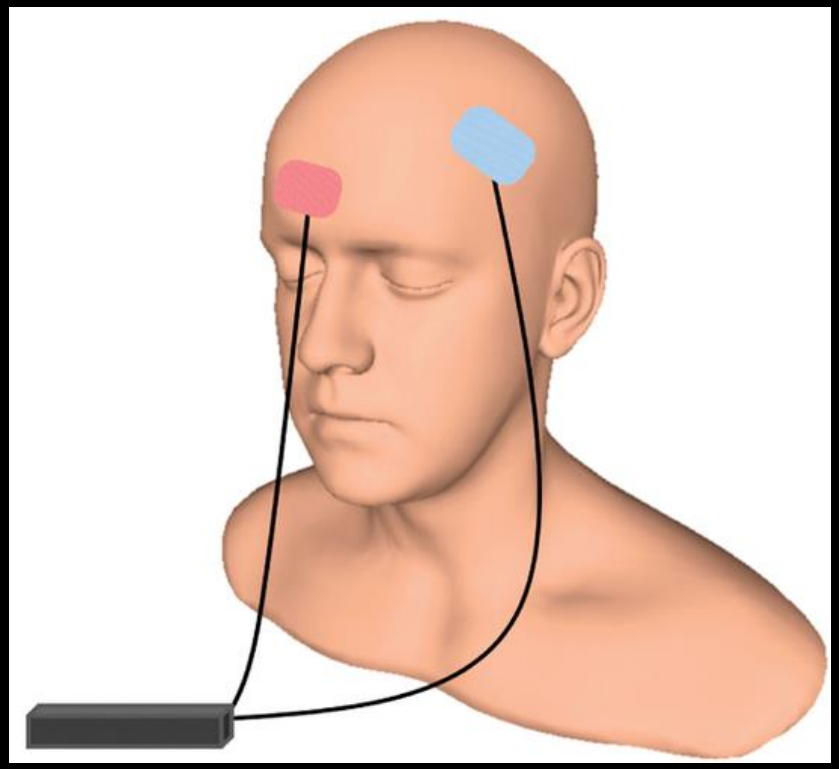
Counting

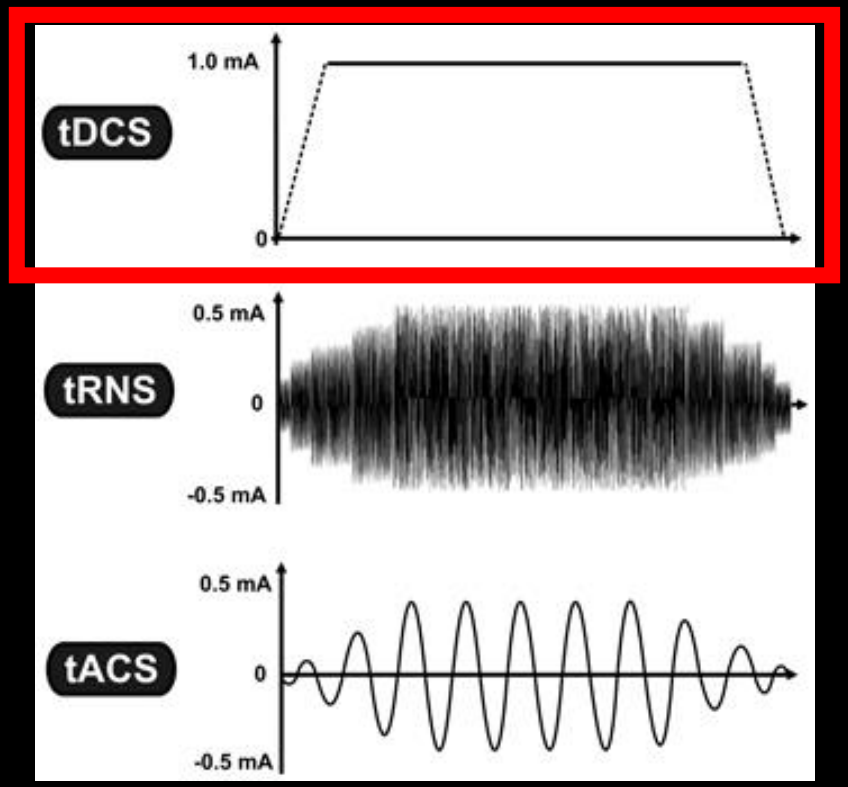
Dual task cost



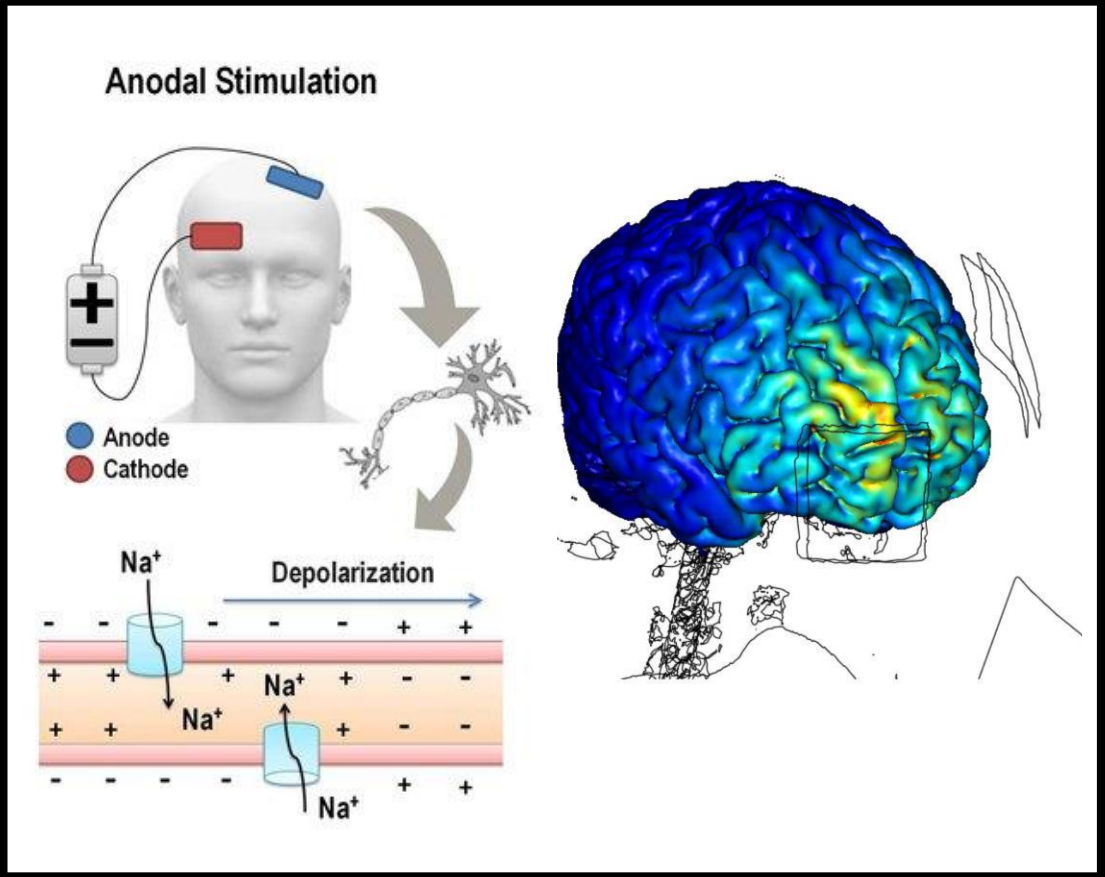
Strategies designed to enhance the cognitive-motor control of gait and balance hold great promise to improve mobility and reduce falls in older adults and those with age-related disease.

Transcranial electrical stimulation (tES) modulates neuronal excitability.





tDCS generates electric fields that polarize neuronal populations.



Polarization alters resting membrane potentials.

Alters likelihood of neuronal firing.

<u>Short-term potentiation</u>: 20 minutes of tDCS modulates excitability for at least one hour.

<u>Long-term potentiation</u>: Repeated sessions induce lasting changes in neuronal anatomy, function, and connectivity.

tDCS generates electric fields that polarize neuronal populations.

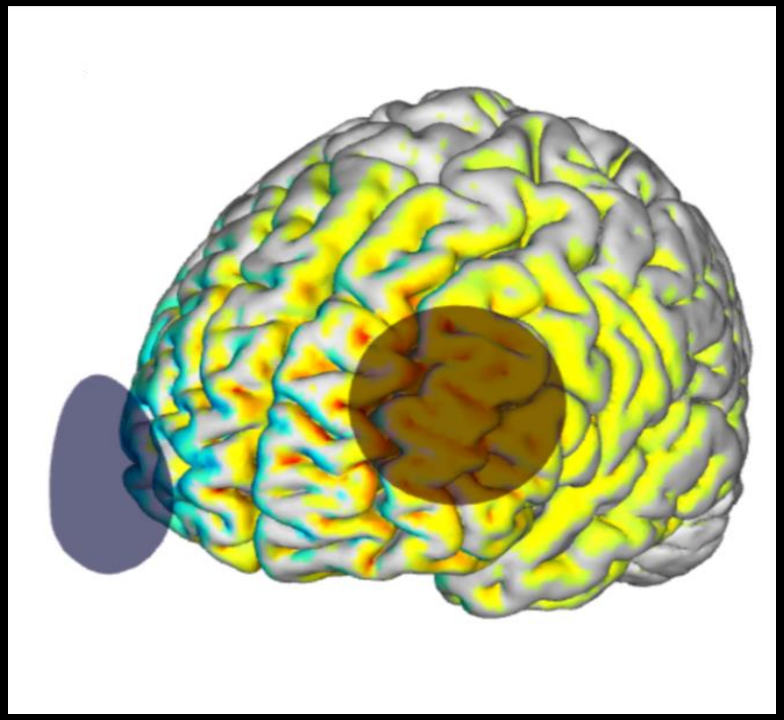
Electrode size

Placement

Direction of flow

Current intensity

Current duration

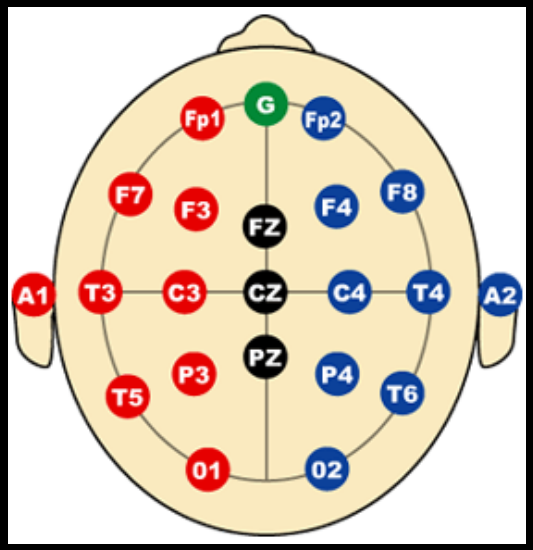


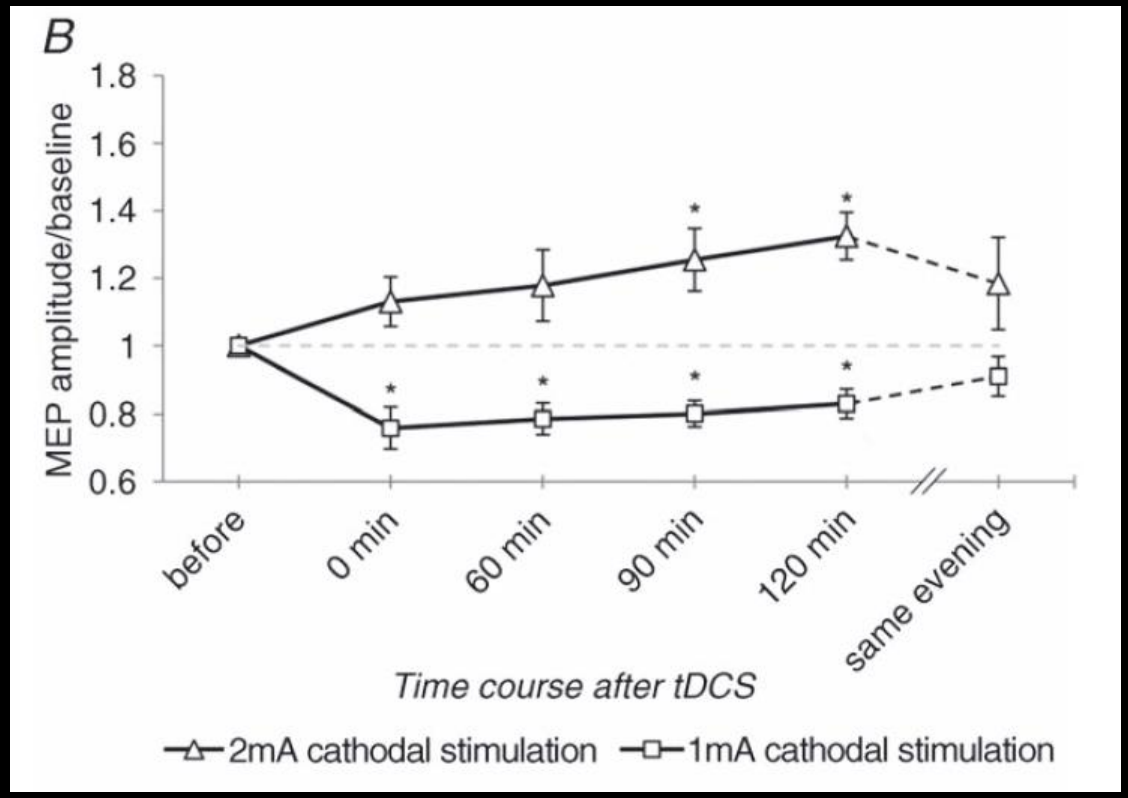
Anatomy:
- Skin
- Skull
- CSF
- gray mater
- White mater

Brain physiology

Brain state
- Off-line (resting)
- On-line

The effects of tDCS depend upon numerous factors.

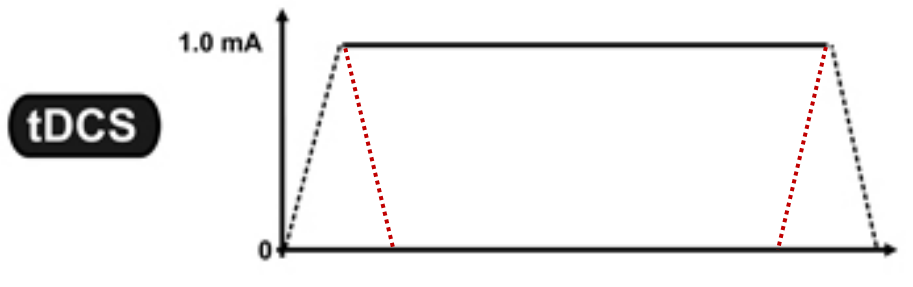




Batsikadze et al, *J Physiol, 2013*

How do we implement tDCS within clinical research?

User experience: Tingling or "pins and needles" associated with ramping up and down.

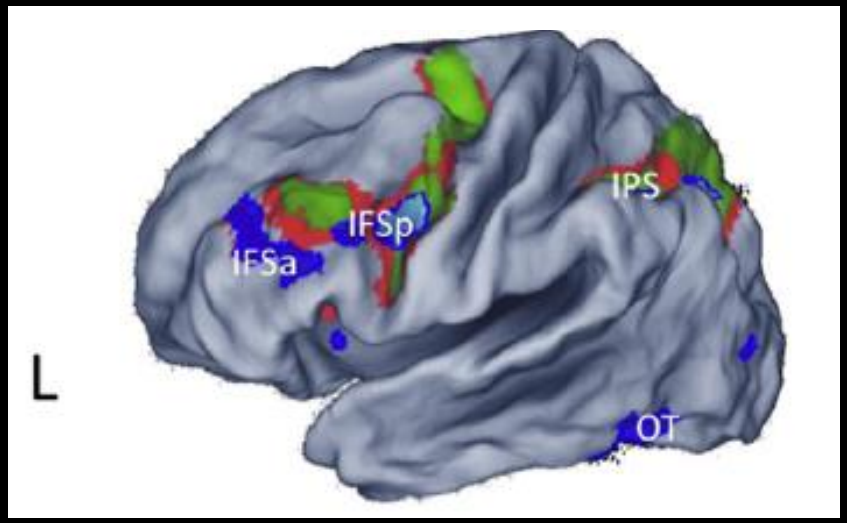


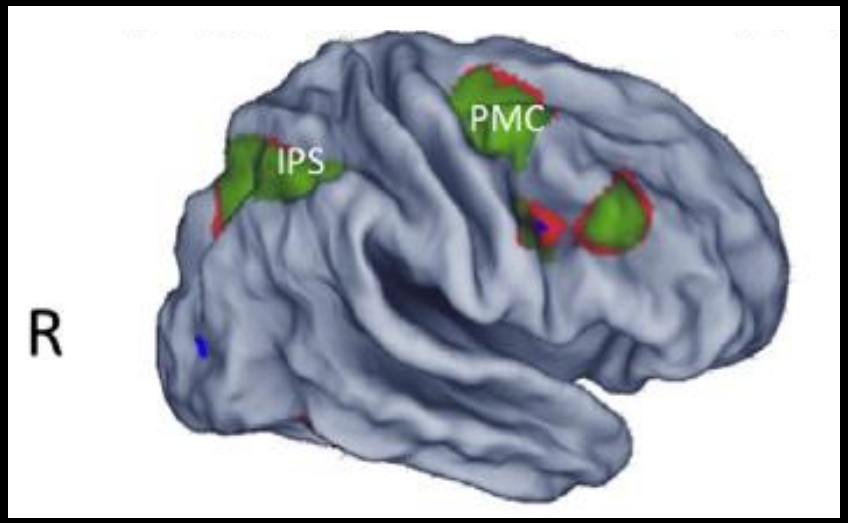
Inactive Sham

Active Sham

- **Compare against different montage**
- **Deliver very-low-level currents that mimic cutaneous sensation but do not significantly affect cortical tissue**

Where should we target?





Single task: Auditory
Single task: Tactile
Dual task

Dual tasking depends upon the activation of numerous brain regions, including the left dorsolateral prefrontal cortex (dlPFC).

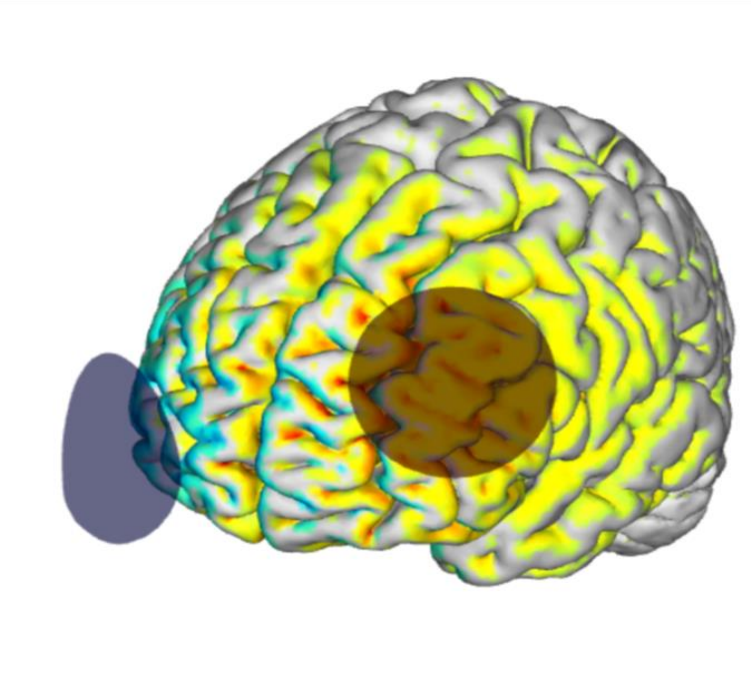
fNIRS research has provided additional supporting evidence.

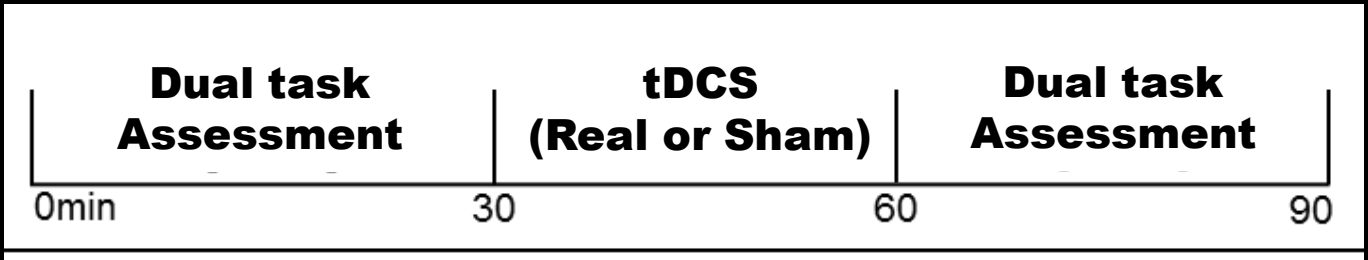
Deprez et al, *Neuropsychologia, 2013*

Single sessions of tDCS targeting the left dlPFC mitigate dual task costs.

tDCS characteristics

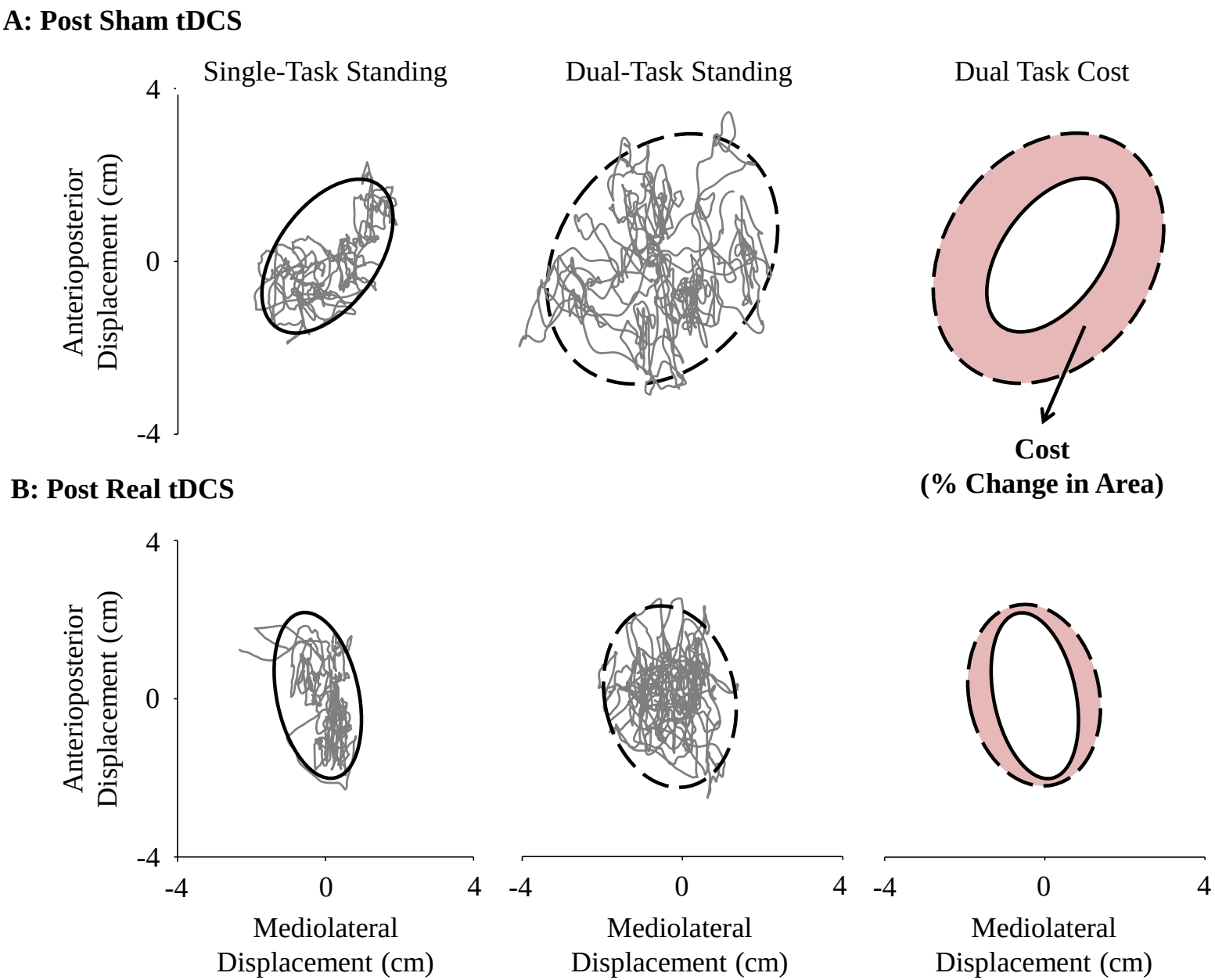
- Two, 5x7cm sponge electrodes
- Anode: F3 on 10-20 EEG system
- Cathode: Contralateral orbit
- 2 mA
- 20 minutes
- Participant at rest



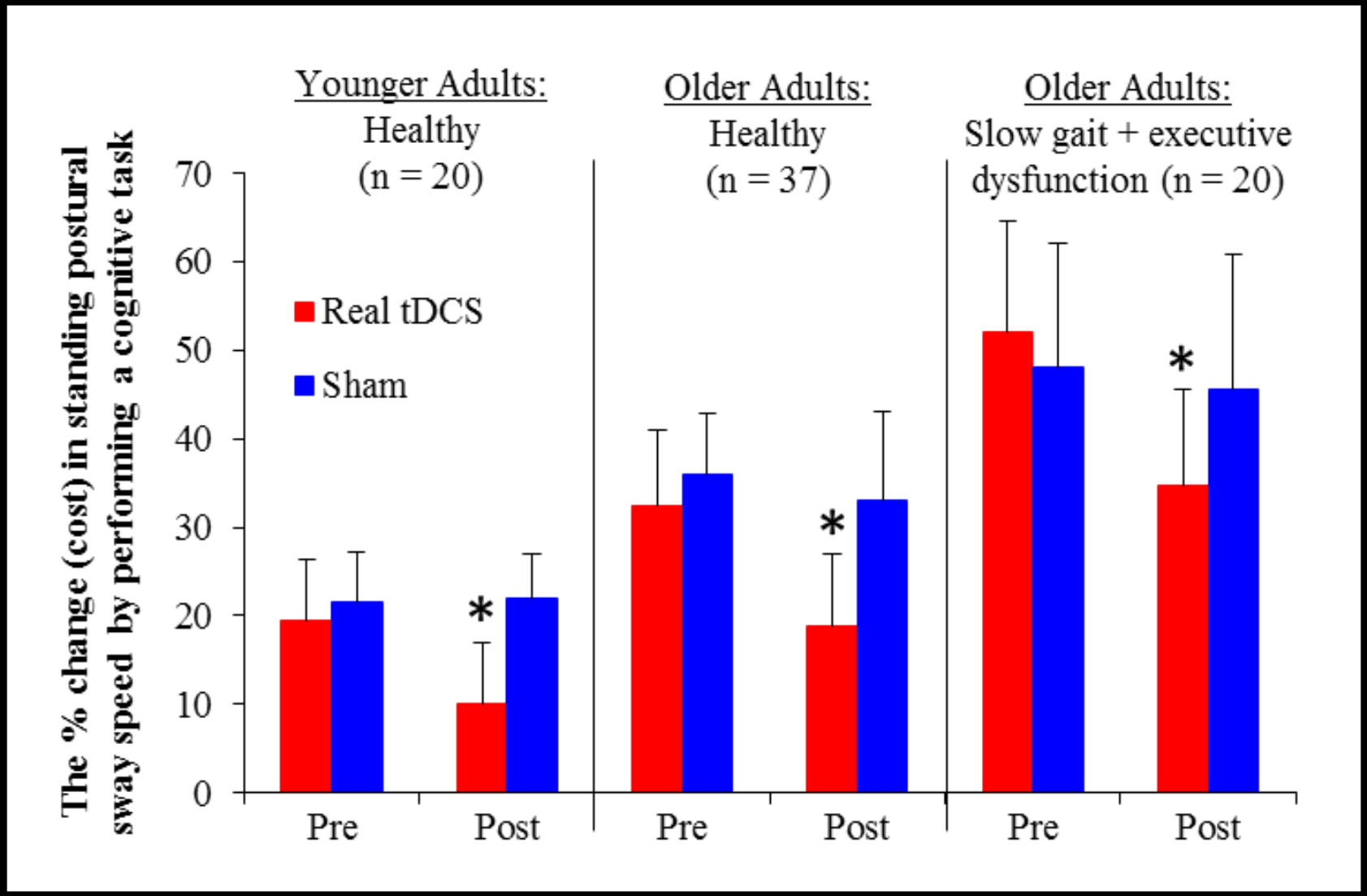


Manor, Pascual-Leone et al, European Journal of Neuroscience, 2014

79 year-old female with previous falls



Single sessions of tDCS targeting the left dlPFC mitigate dual task costs.



Manor et al Euro J of Neurosci 2014; J Cogn Neurosci 2016; Annals of Neurology 2021

Do multiple sessions inducing lasting effects?

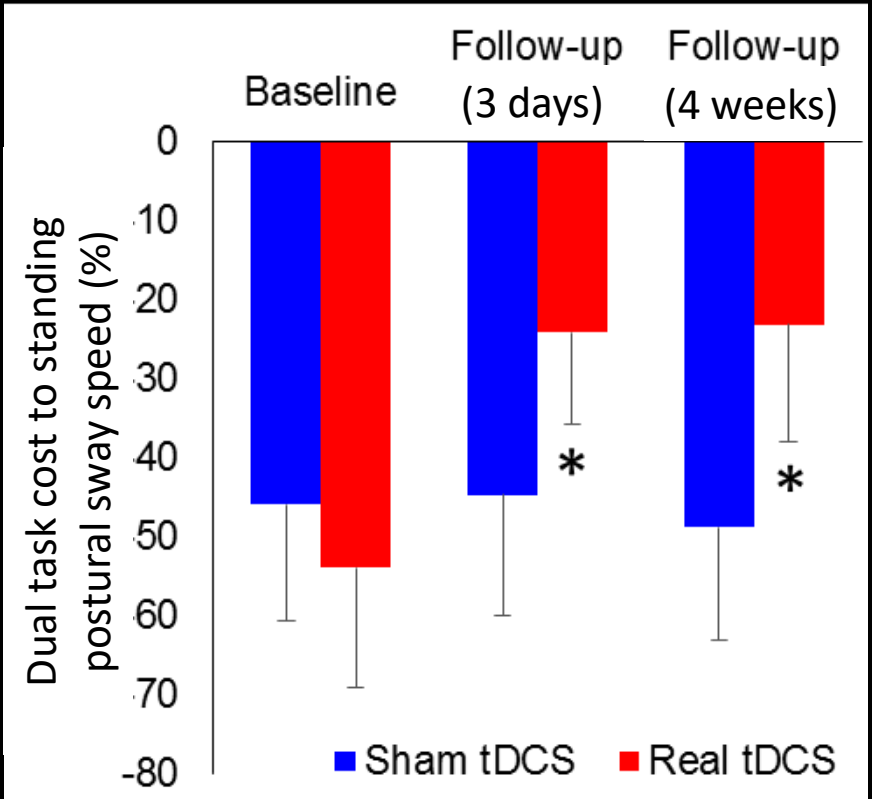
- 20 older adults with slow gait and mild executive dysfunction

tDCS versus inactive sham

10, once-daily sessions

Baseline, immediate, 4-week follow-up

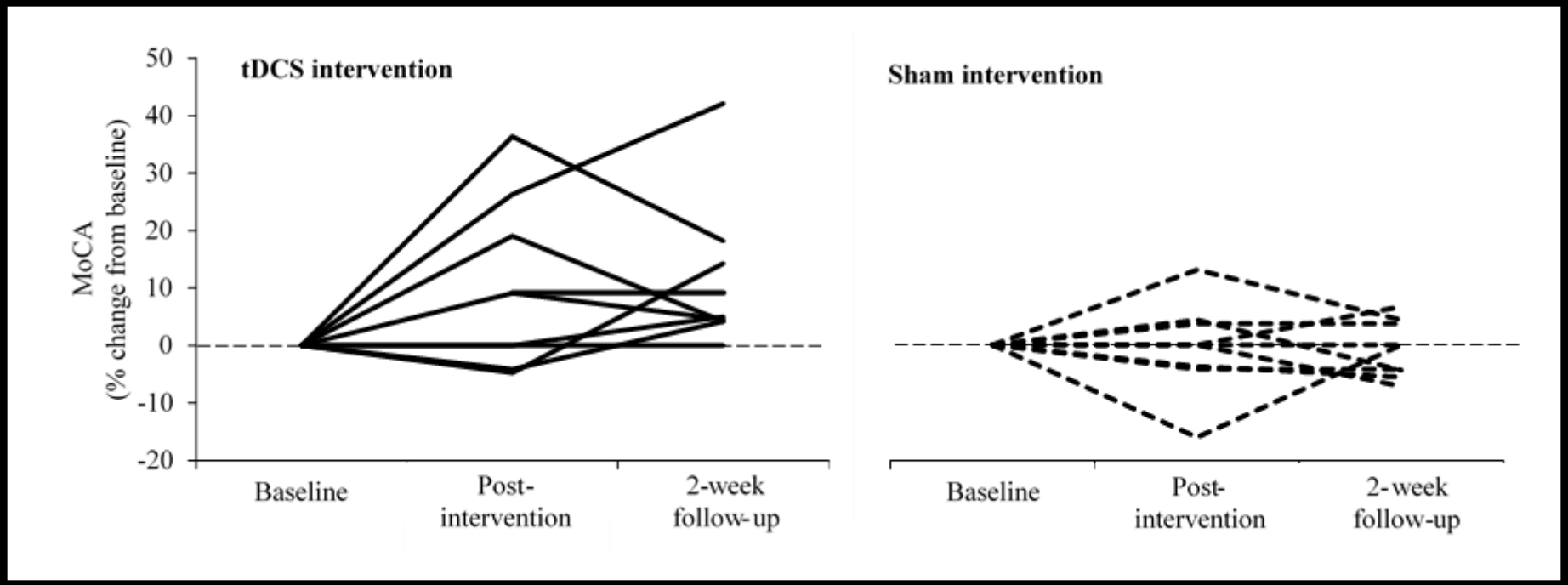
Functional assessments + fMRI



Trends ($p < 0.1$) towards increased performance were also observed in:
- Timed Up-and-Go (TUG) test of mobility
- Preferred gait speed

Manor et al, Neuro Rehab. Repair, 2018

Multiple sessions of tDCS induced lasting improvements in cognitive function.

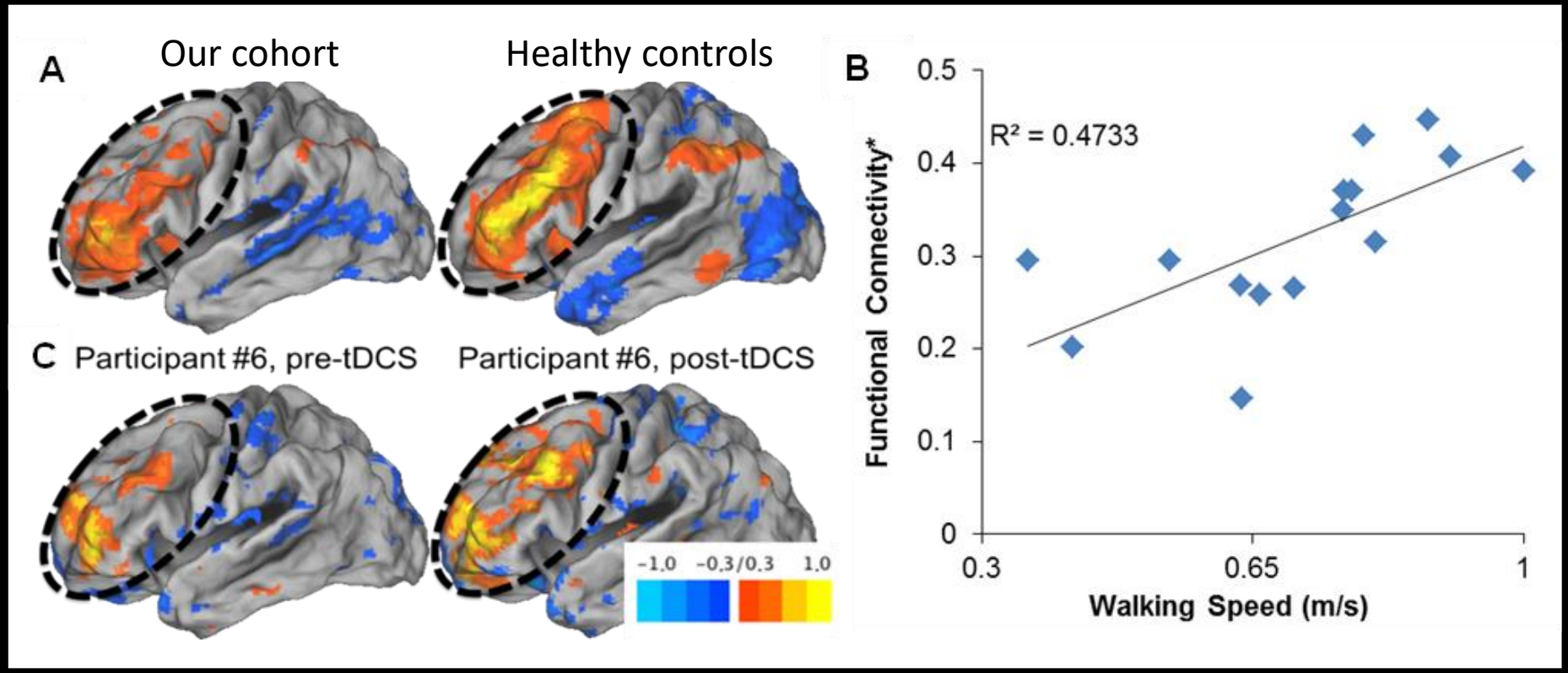


tDCS-related improvements were limited to the “executive function” sub-score.

Manor et al, Neuro Rehab. Repair, 2018

Multiple sessions of tDCS appeared to alter brain function as measured by resting-state fMRI.

Functional connectivity: Fronto-parietal control network



tDCS appears to induce meaningful changes in brain function that are directly related to improvements in gait and balance.

Zhou et al, Neuroscience Letters. Repair, 2018

Higher-level control of gait and balance in older adults

Transcranial current stimulation (tCS) – quick overview

tDCS holds promise to improve gait and balance in older adults

Limitations / needs for future research: Optimal targets; Personalization; Accessibility

tDCS may improve cognitive-motor function in older adults, but there are major challenges:

What are the optimal targets?

High inter-subject variance in effectiveness.

tDCS is not accessible to those with mobility restrictions.

Is the left dlPFC the best and only target?
Is tDCS the best and only form of stimulation?

Motor output and coordination

Sensation

Sensory integration

Cognition

Mood

Does simultaneously targeting the sensorimotor cortex amplify effects of left dlPFC stimulation?

57 older adults without overt illness or disease completed 4 visits.

Dual tasking was assessed before and after "multi-target" tDCS with the following targets:

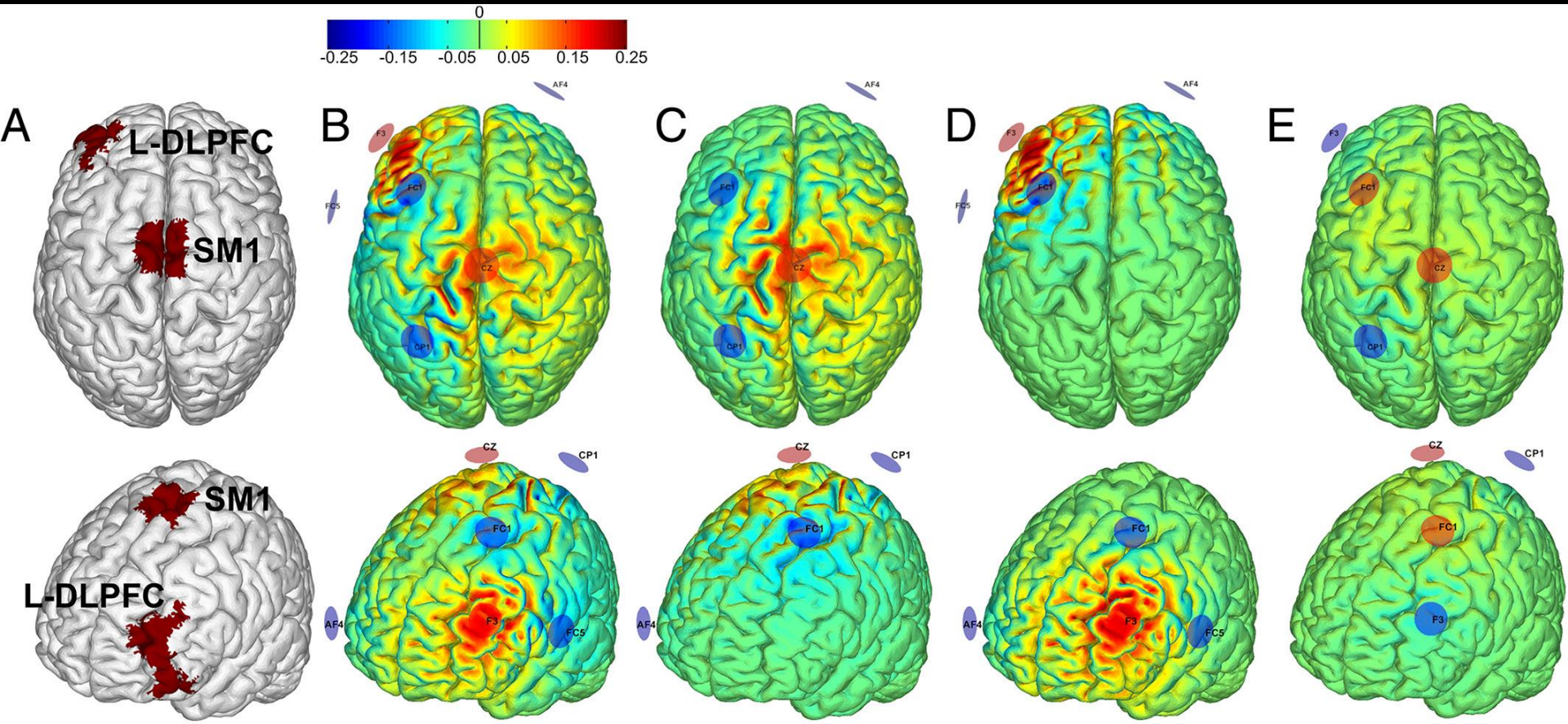
1. Left dlPFC only
2. Bilateral M1 only
3. Left dlPFC + bilateral M1
4. Actisham

Pre and post-stimulation assessments:

1. Dual task gait and standing balance
2. Cognitive task performance
3. 32-channel EEG during standing balance

Manor, Zhou et al, Annals of Neurology, 2021

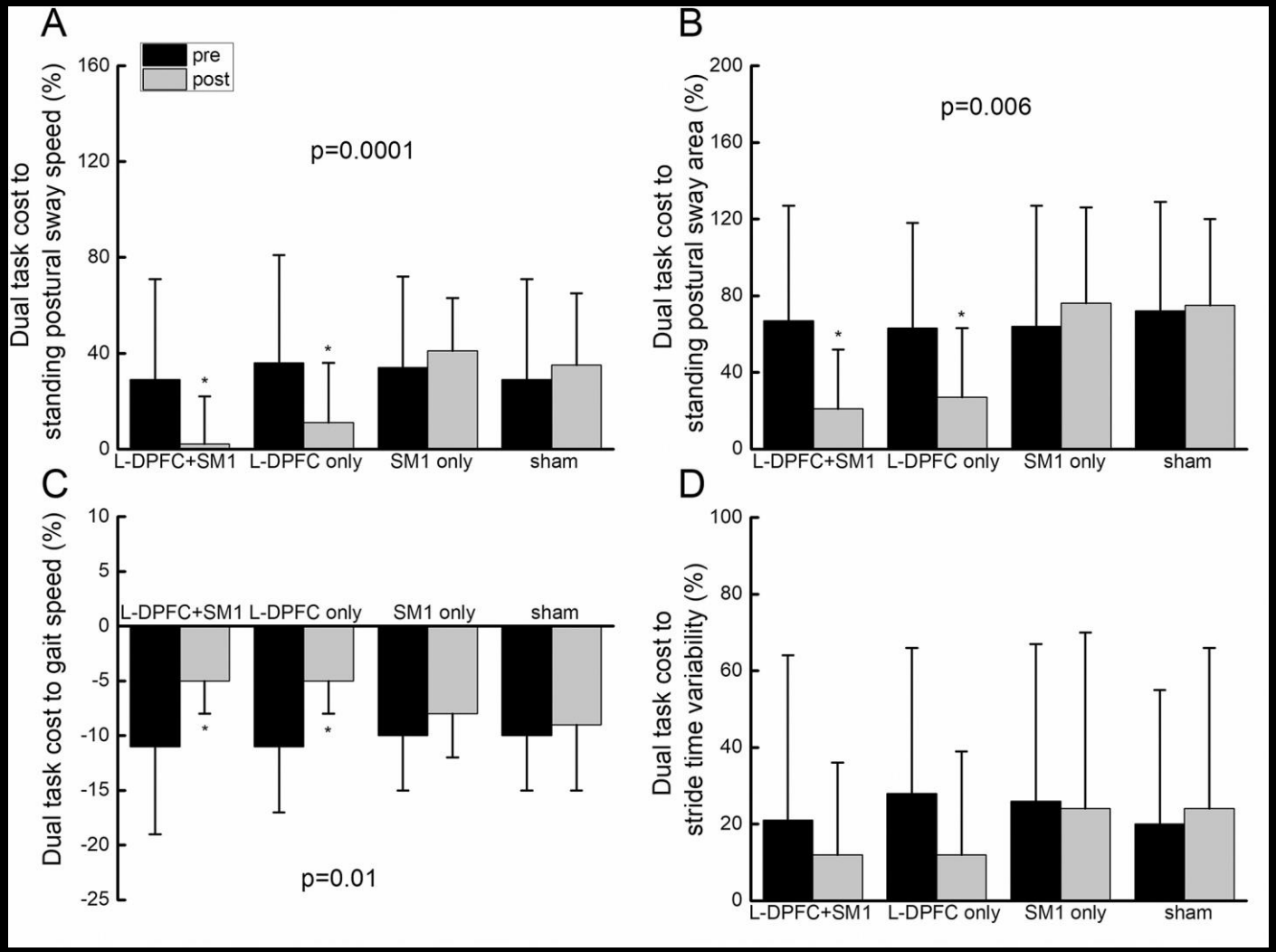
Modeling was used to target the left dlPFC, M1, both, or neither.



Target ROI *En* (V/m)	L-DLPFC+SM1	SM1 only	DLPFC only	Acti-sham
L-DLPFC	0.06	-0.01	0.07	-0.01
SM1	0.03	0.04	0	0.01

Manor, Zhou et al, Annals of Neurology, 2021

tDCS targeting the left dlPFC, with or without M1, mitigated dual task costs to gait and balance.



Manor, Zhou et al, Annals of Neurology, 2021

Was blinding achieved, and were there placebo effects?

- Blinding:
  - The proportion of guesses (real, sham) was not different from that expected by chance.
  - There were no group-level changes in the confidence of guesses from visit to visit.
  - Within each stim condition, the order of administration did not influence the number of participants who guessed “real.”

- Within each condition, subjective guess did not influence the effects of stimulation on gait or balance outcomes.

Manor, Zhou et al, Annals of Neurology, 2021

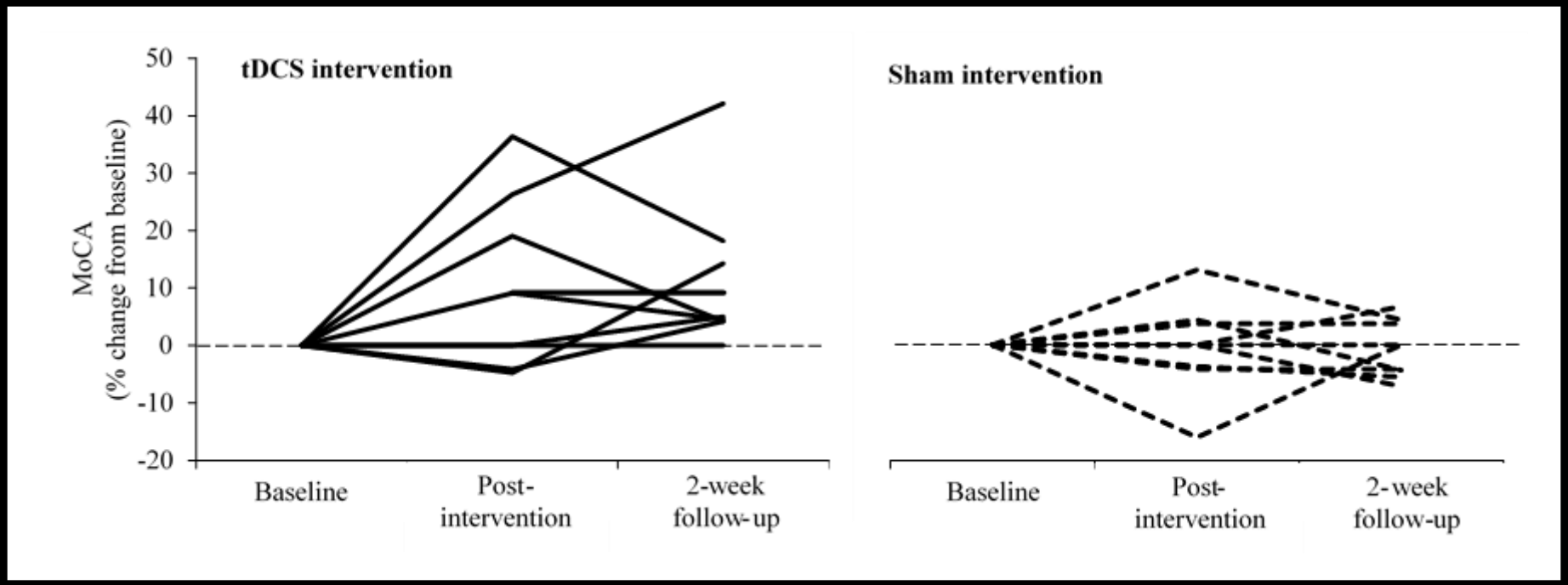
tDCS may improve cognitive-motor function in older adults, but there are major challenges:

What are the optimal targets?

High inter-subject variance in effectiveness.

tDCS is not accessible to those with mobility restrictions.

What's causing such high inter-subject variability?



What's causing such high inter-subject variability?

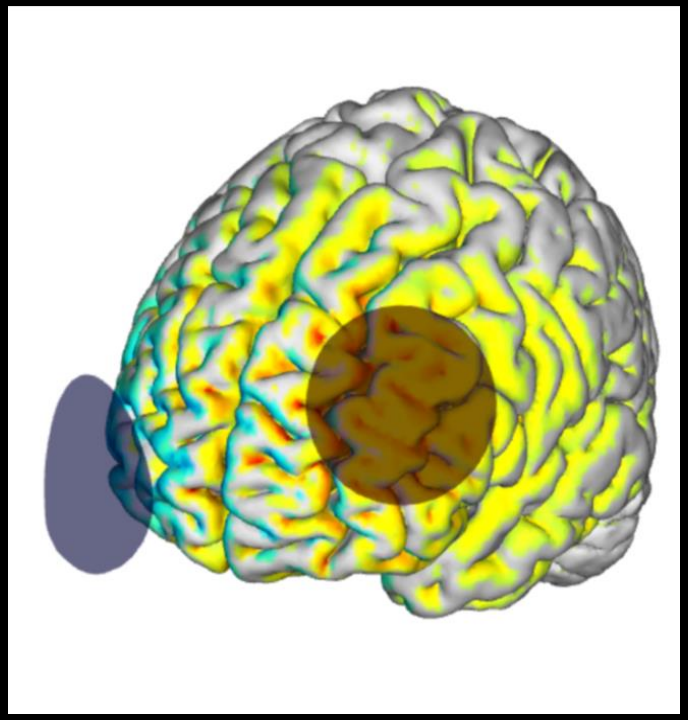
Electrode size

Placement

Direction of flow

Current intensity

Current duration



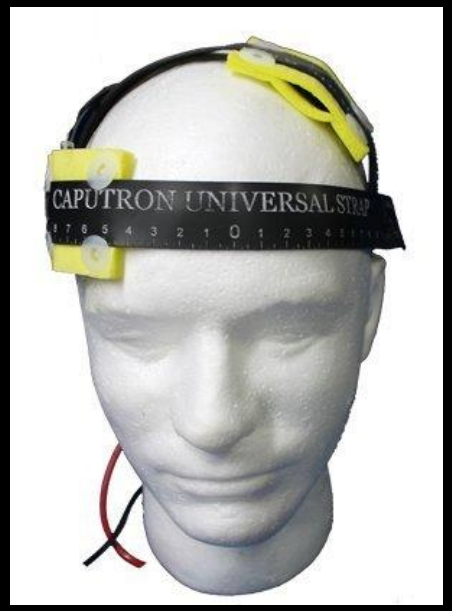
Anatomy:
- Skin
- Skull
- CSF
- gray mater
- White mater

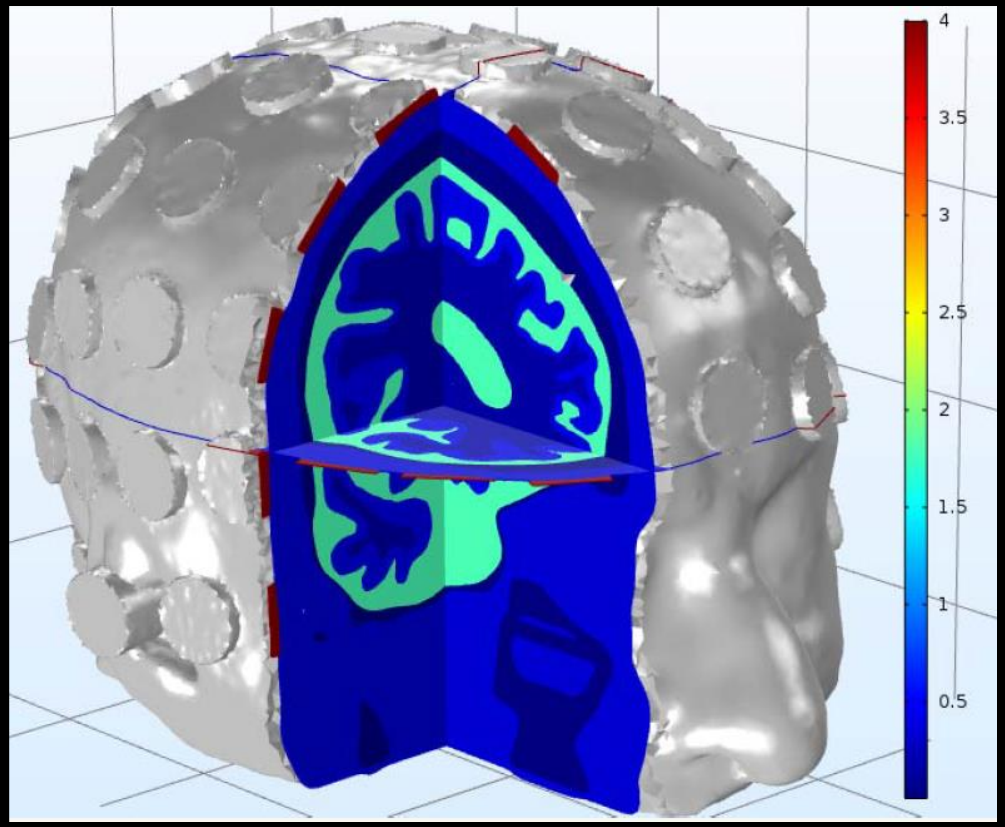
Brain physiology

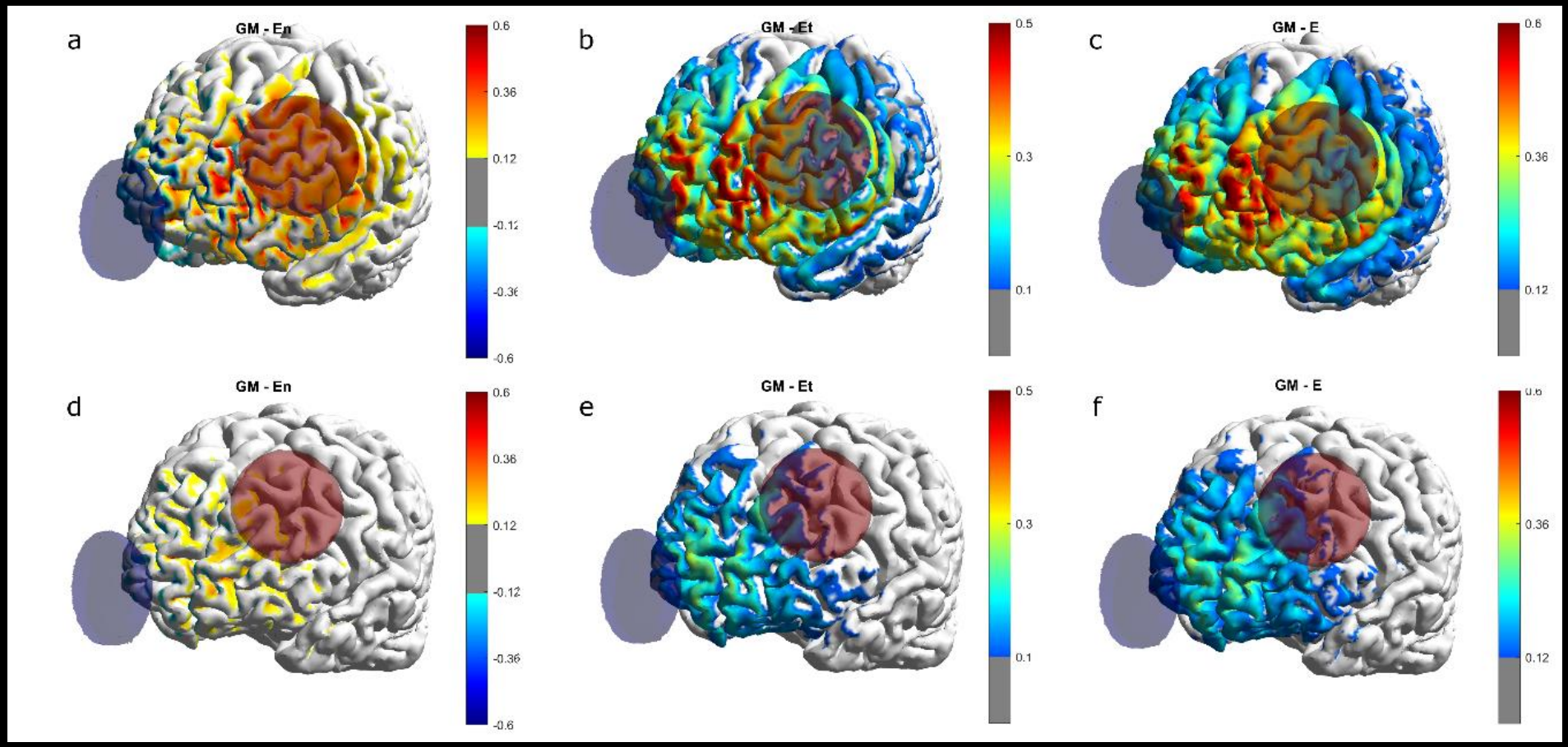
Brain state
- Off-line (resting)
- On-line

Biological aging—especially in the presence of disease—alters brain structure and function, and thus, the flow and effects of tDCS.

We can perform e-field modeling on individual MRIs to understand, personalize, and optimize tDCS interventions.

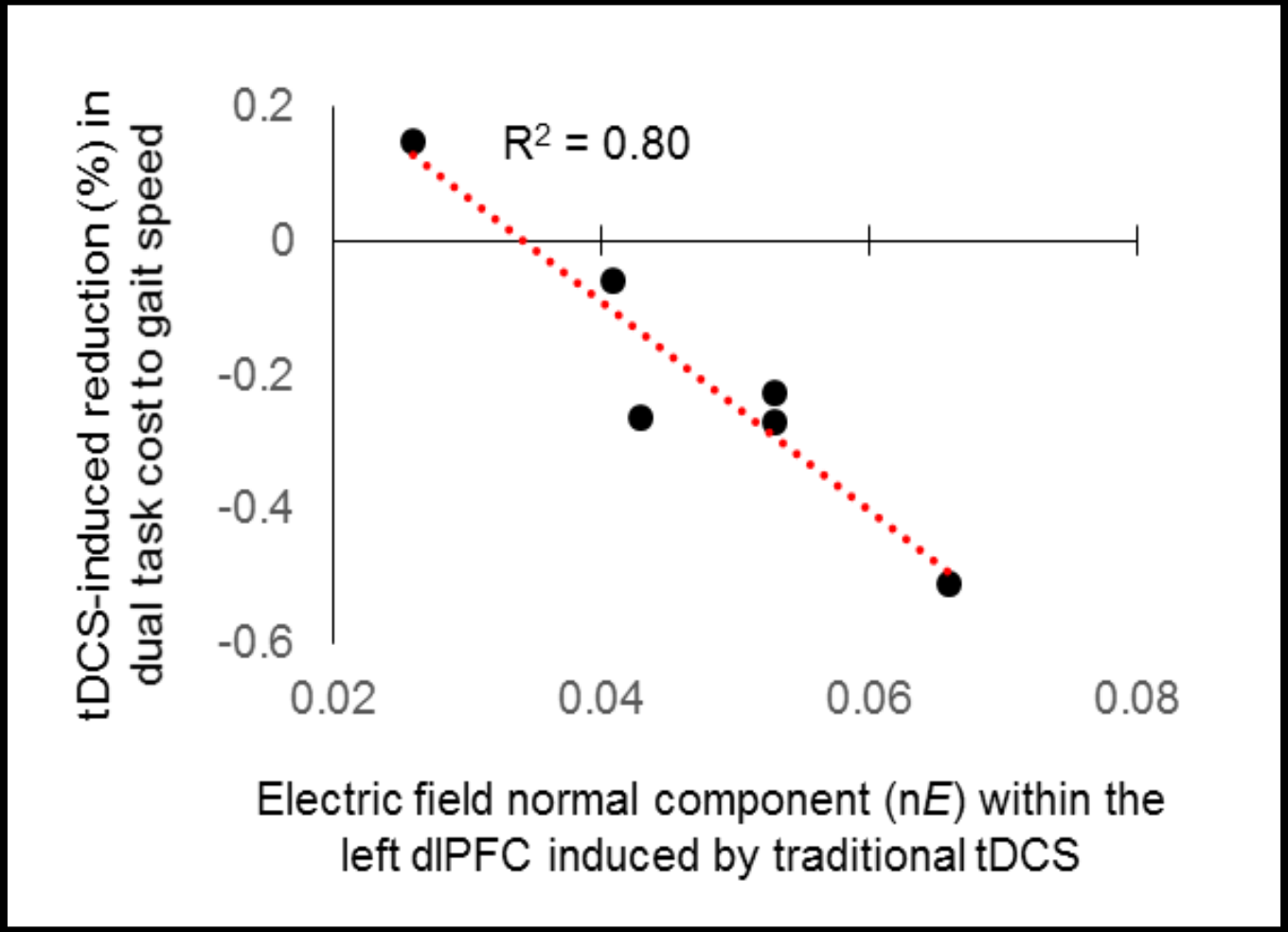




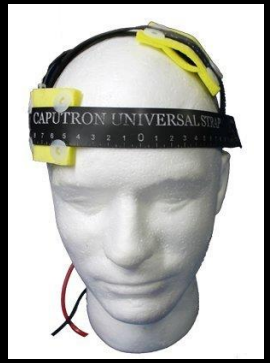


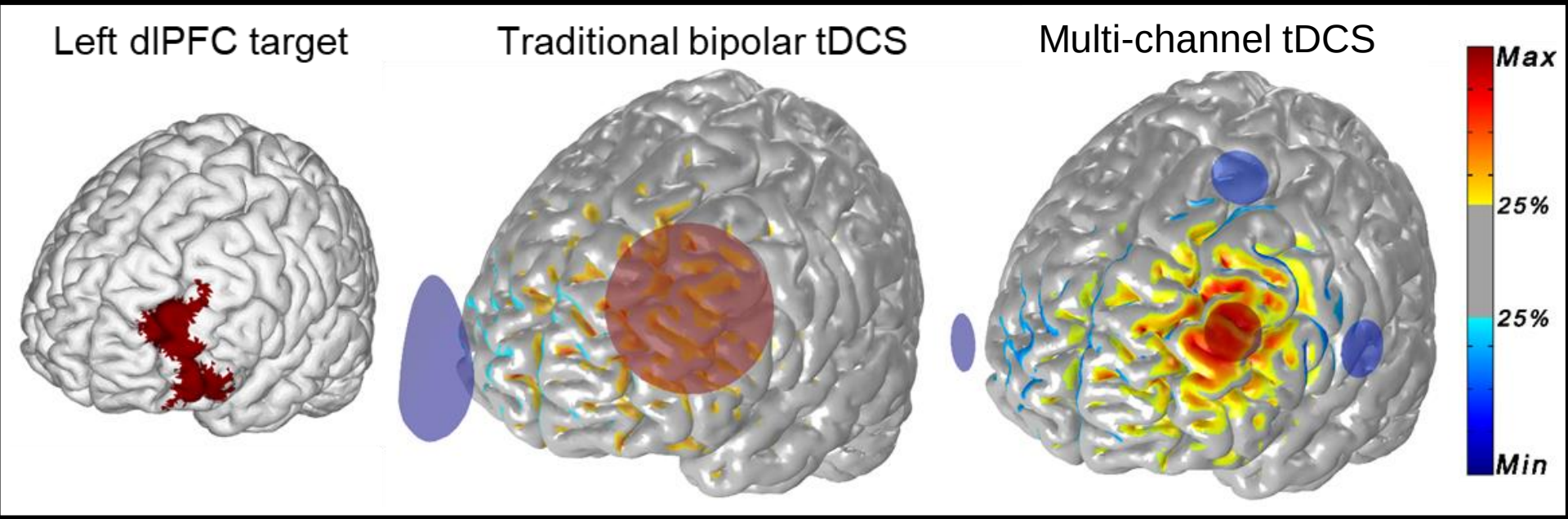
E-field distribution in the bipolar montage for the subject with highest (top row, a-c) and lowest (bottom row, d-f) ⟨E_n ⟩_(left DLPFC). The top 1st column (a) shows the distribution of En; the 2nd column (b) the distribution of Et and the 3rd (c) the E-field's magnitude. All values (in V/m) are plotted using a common scale across montages (but different for each E-field component) which was thresholded to 20% of the maximum value. Anodes are shown in red and cathodes in blue.

On-target 'dose' of tDCS varies considerably across participants, and may correlate with observed responses.

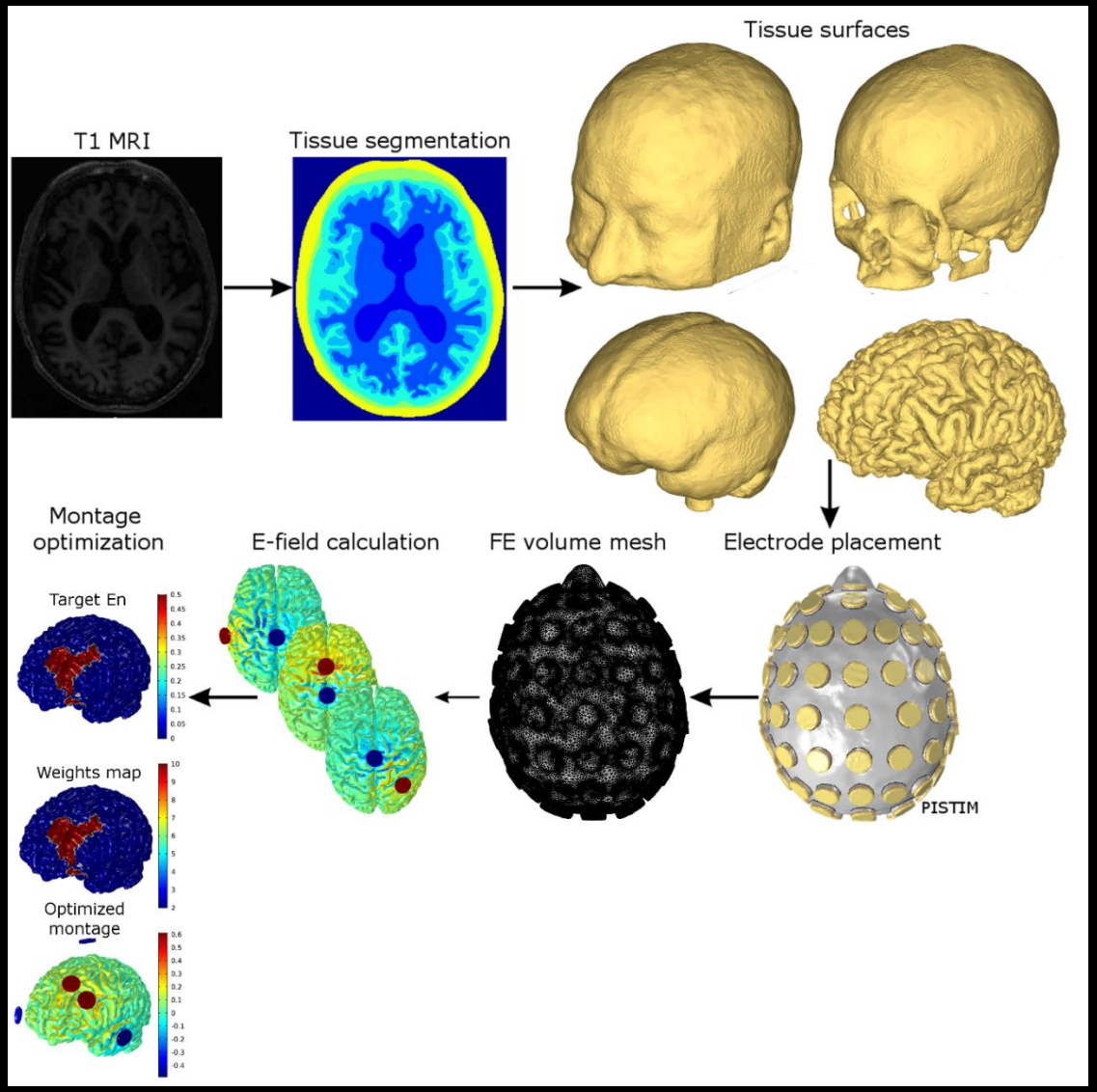


Advances in tDCS administration and modeling technology now enables more precise targeting.





tES can be developed to optimize on- and off-target current flow for each individual.



Individualized Stimulation To Improve Mobility (I-STIM) trial (on-going).

For each subject, we will develop a stimulation protocol to maximize flow to their left dlPFC.

The sham protocol will use the same electrode placement, but designed to mimic skin sensations with minimal influence on cortical tissue.

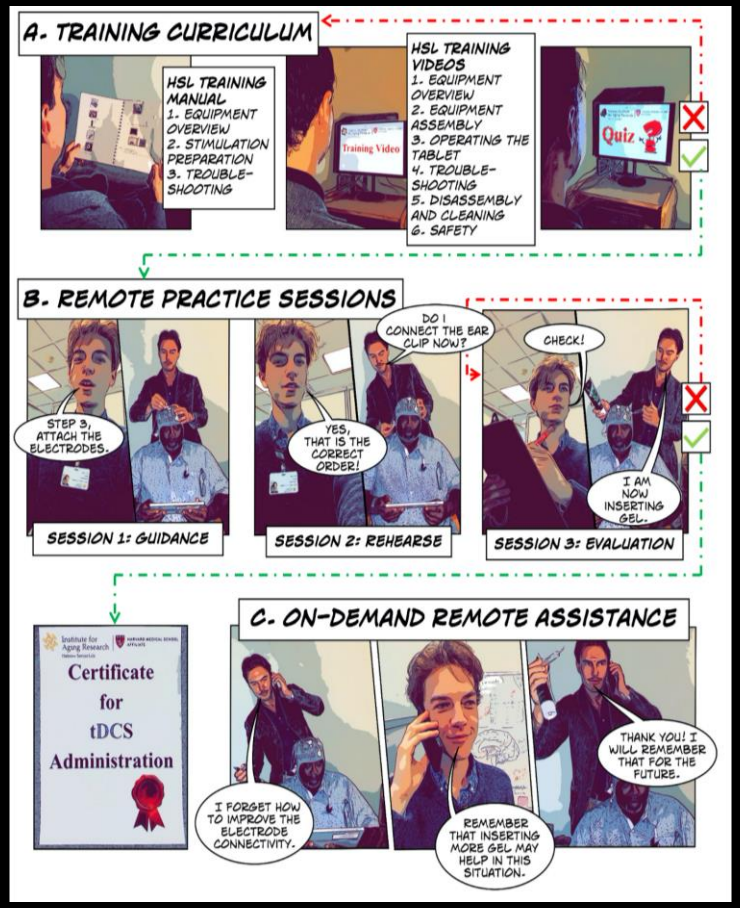
tDCS may improve cognitive-motor function in older adults, but there are major challenges:

What are the optimal targets?

High inter-subject variance in effectiveness.

tDCS is not accessible to those with mobility restrictions.

Remotely-supervised, caregiver-led, home-based tCS is safe and feasible in older adults.



Recruiting user/administrator "pairs"

↓

tCS prescribed by research team

↓

Pair receives in-person training to use custom Starstim™ and tablet

↓

Staff observes sessions until administrator is proficient

↓

Administrator leads intervention with remote staff supervision

↓

Side effects queried before/after stimulation via tablet

To date: >40 'pairs'; >2000 sessions completed.

Brechet et al, Frontiers in Neurology, 2021.

5 take-home messages:

1. In older adults, gait and balance are complex behaviors that depend upon numerous cognitive functions and underlying brain networks.

2. Dual task paradigms provide insight into brain health and clinically-meaningful outcomes.

3. tDCS targeting cognitive-motor brain regions appears to improve dual tasking, mobility and cognitive function, even in vulnerable older adults. Long-term effects are unclear.

4. The aging process undoubtedly alters the flow and effects of tDCS on the brain.

5. Modeling, personalization, and remote administration of tCS are critical to advancing this promising tool and potential intervention.

Thank you!

Mentors:
- Lewis Lipsitz MD
- Alvaro Pascual-Leone MD PhD
- Jeff Hausdorff

Mobility and Brain Function Program:
- Junhong Zhou PhD
- Amy Lo PhD
- Azizah Jor’dan PhD
- Peggy Gagnon RN
- Nicole LeGanke BS
- Wanting Yu MS
- Ali Ludington BS

Collaborators:
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- Talia Herman PhD
- Moria Dagan MS
- Giulio Ruffini PhD