A more accurate and reliable method to rehabilitate sports related TBI patients

Timofei Tunekov
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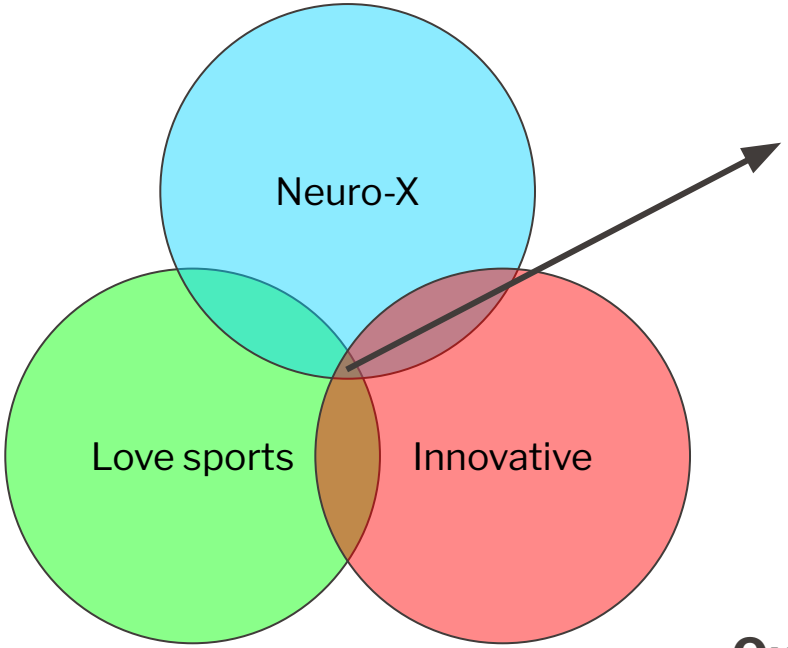
Introduction



Sports related chronic TBI

- Neurological lesion
- Mostly affects contact sport ex-athletes
- Few research done on subgroup

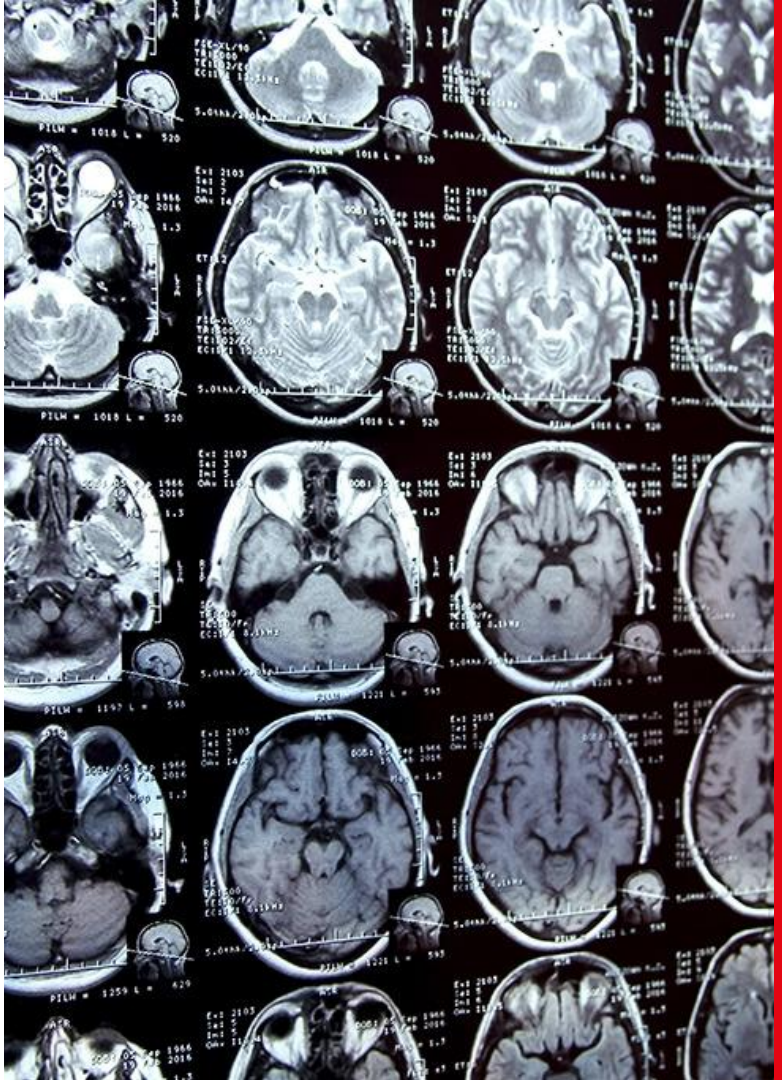
Question:

Can striatal transcranial temporal interference stimulation of ex-athletes suffering from sports related TBI increase their performance in a proficient motor skill ?

Overview

- ❏ Biological background
- ❏ Transcranial temporal interference stimulation
- ❏ Task design
- ❏ Study design
- ❏ Discussion
- ❏ Conclusion

Alexandra Psaltis



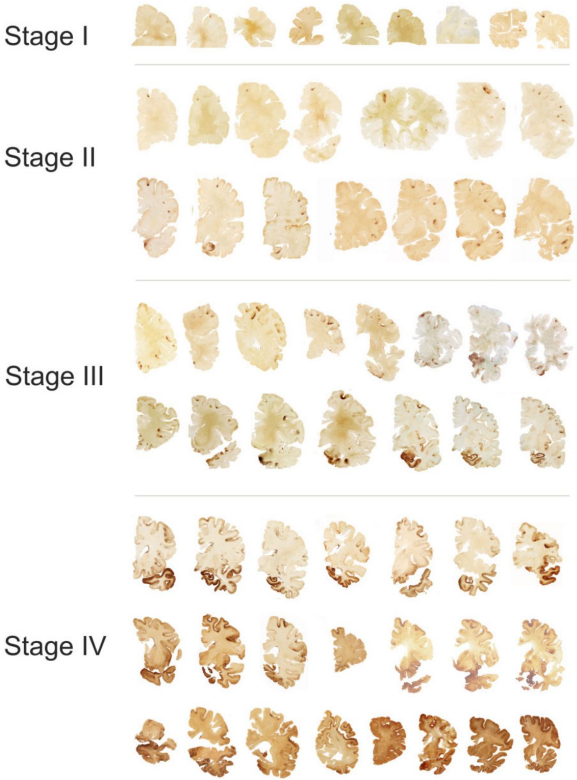
Biological background

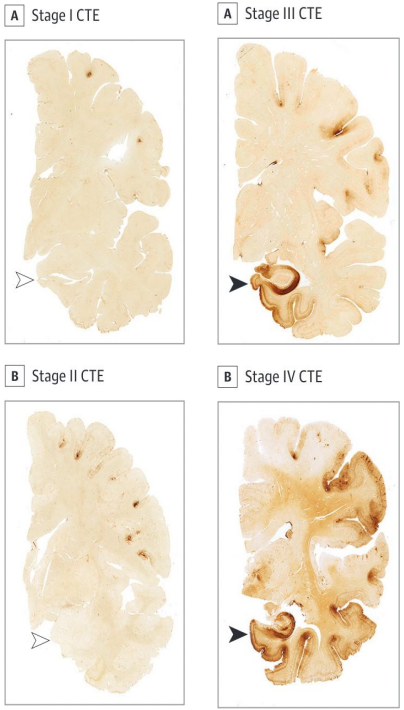
Sports related TBI

Neurodegeneration

Striatal motor function

Sports-related TBI: symptoms and pathology





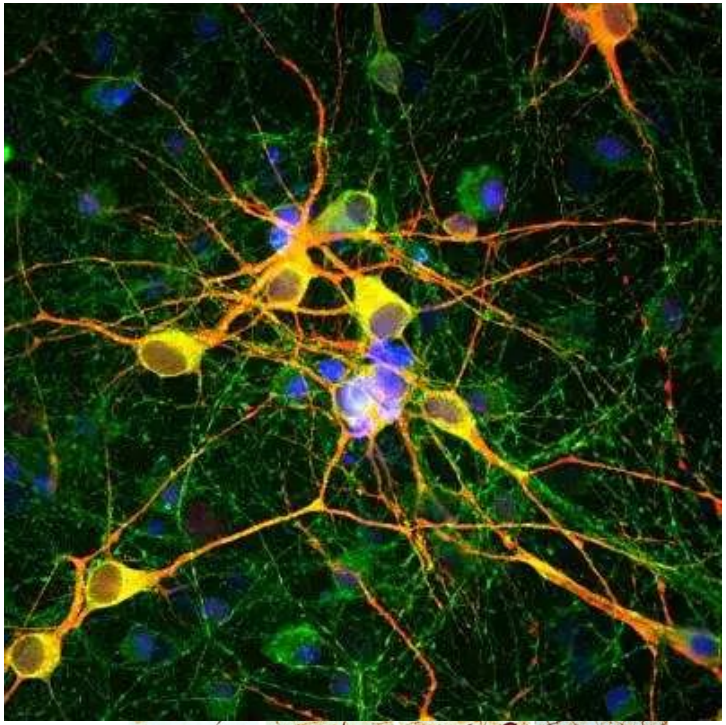
Symptoms in early stages: irritability, impulsivity, aggression, depression, short-term memory loss

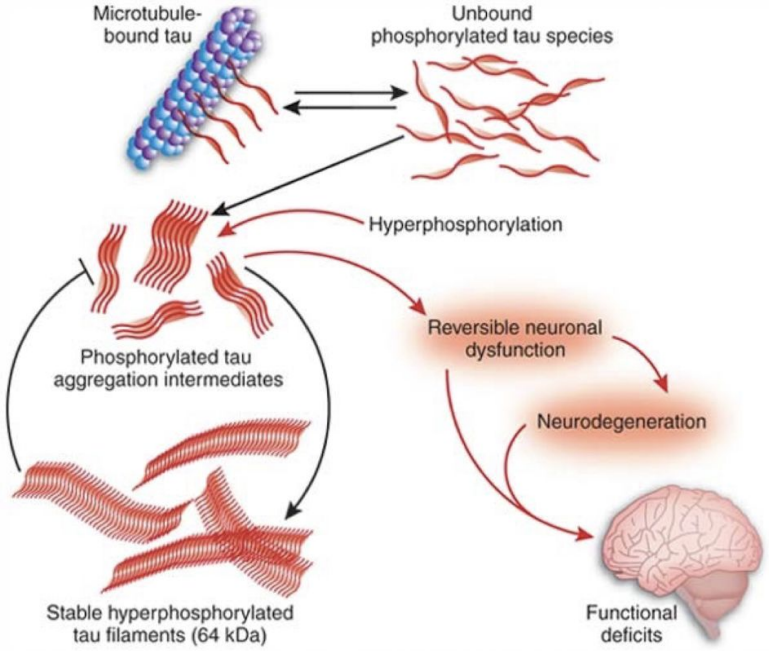
Symptoms in advanced stages: dementia, gait and speech abnormalities, parkinsonism

Symptoms in late stages: very similar to Alzheimer's disease or frontotemporal dementia or motor neuron disease

McKee (2015). The Neuropathology of Chronic Traumatic Encephalopathy.
Mez (2017). Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football.

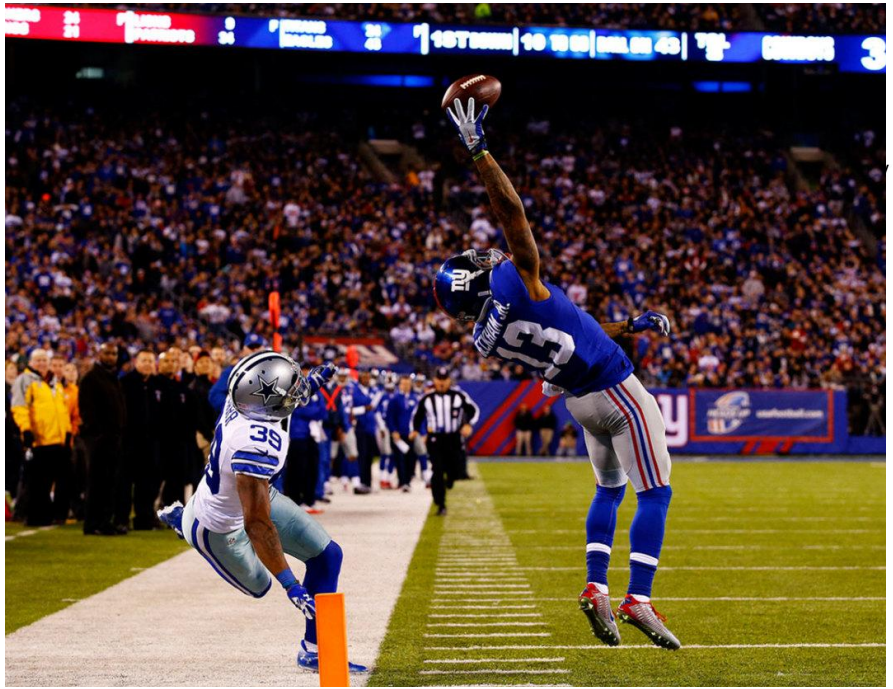
Sports-related TBI : symptoms and pathology





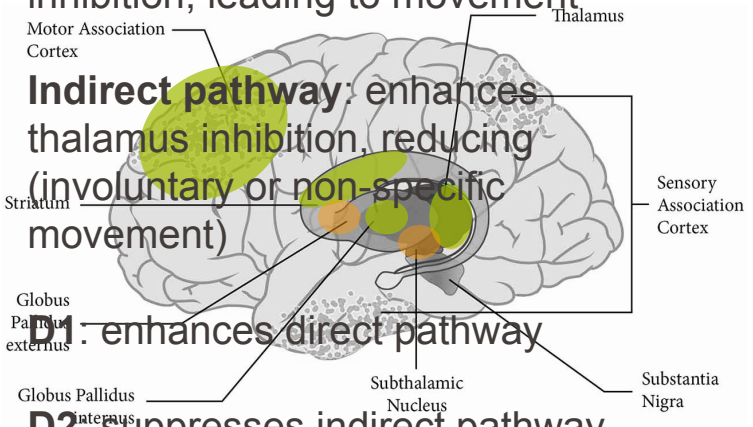
McKee (2012). The spectrum of disease in chronic traumatic encephalopathy.

Striatum: neuromotor function & motor learning



Direct pathway: reduces thalamus inhibition, leading to movement

Indirect pathway: enhances thalamus inhibition, reducing (involuntary or non-specific movement)



D1: enhances direct pathway

D2: suppresses indirect pathway

Transcranial temporal interference stimulation (tTIS)

Concept

Pattern of stimulation

Concurrent EEG recording

Transcranial Temporal Interference Stimulation (tTIS)

tTIS Concept:

- High frequencies f_1 and $f_2 = f_1 + \Delta f$ are applied, with Δf in the neural response range

Fields Superposition:

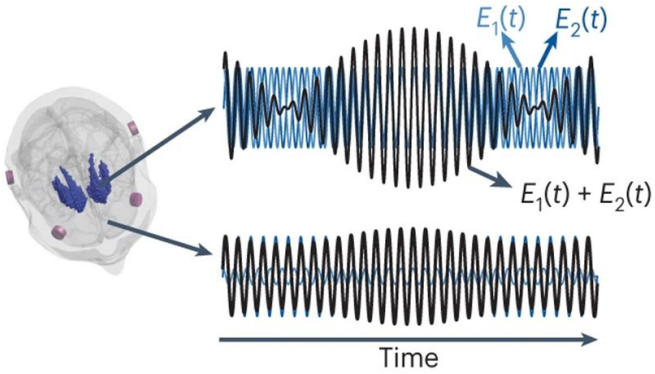
- Fields superposition result in frequency $(f_1 + f_2)/2$ with modulation at Δf

Deep Stimulation:

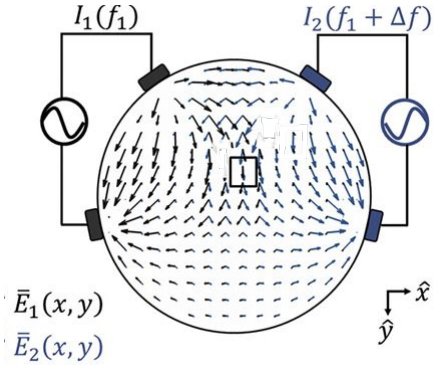
- Amplitude Modulation peak can be formed deep in the brain, distant from electrodes

Control of Location:

- Focus of the envelope location depends on electrodes configuration and waveforms properties



tTIS of striatum [1]



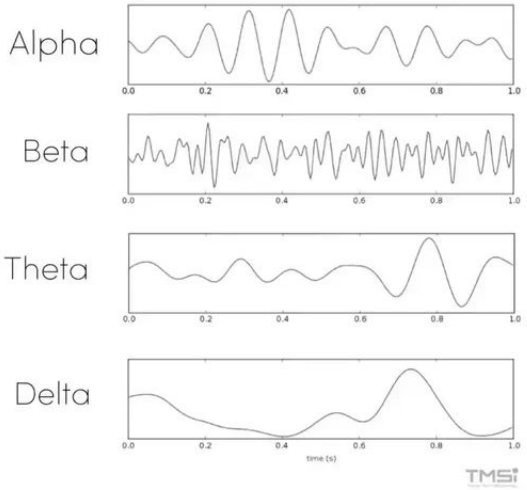
Electric fields during tTIS of hippocampus [2]

[1] Wessel et al. (2023)
[2] Grossman et al. (2017)

Pattern of Stimulation

Intermittent Theta-burst stimulation:

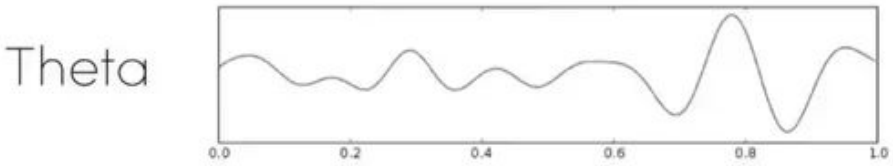
- This form of stimulation has been shown to induce long-term potentiation (LTP)-like effects [1,2,3]
- Theta-burst patterned striatal tTIS increased activity in the striatum and associated motor network [4]
- Enhanced motor performance [4]
- This method employs short, rapid bursts of pulses based on theta rhythm frequencies (around 5 Hz), which correspond to natural brain activity frequencies

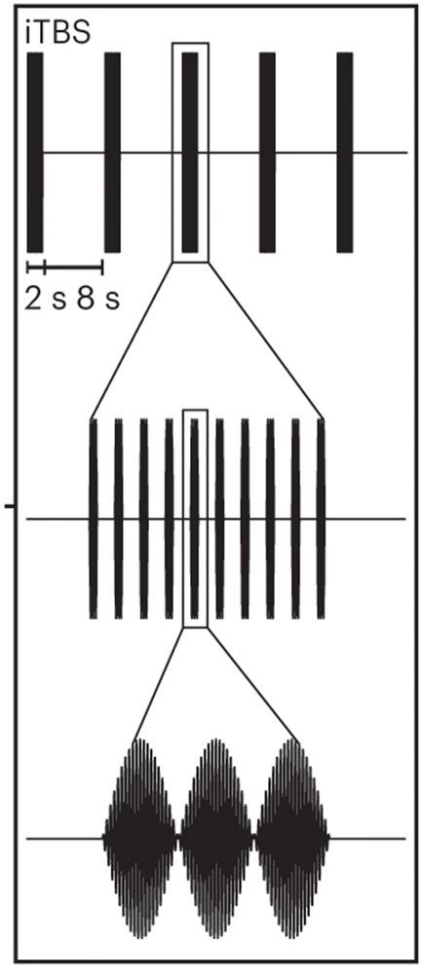


[1] Larson et al. (1986)
[2] Huang et al. (2005)
[3] Larson et al. (2015)
[4] Wessel et al. (2023)

Stimulation Protocol

- Beat frequency of 100 Hz for LTP-like effects
- 2-s trains of stimulation every 10 seconds
- Each train: 10 bursts at 5 Hz
- Each burst: 3 pulses at 100 Hz beat frequency
- During the interburst and intertrain intervals (8 s), non amplitude-modulated HF stimulation is applied

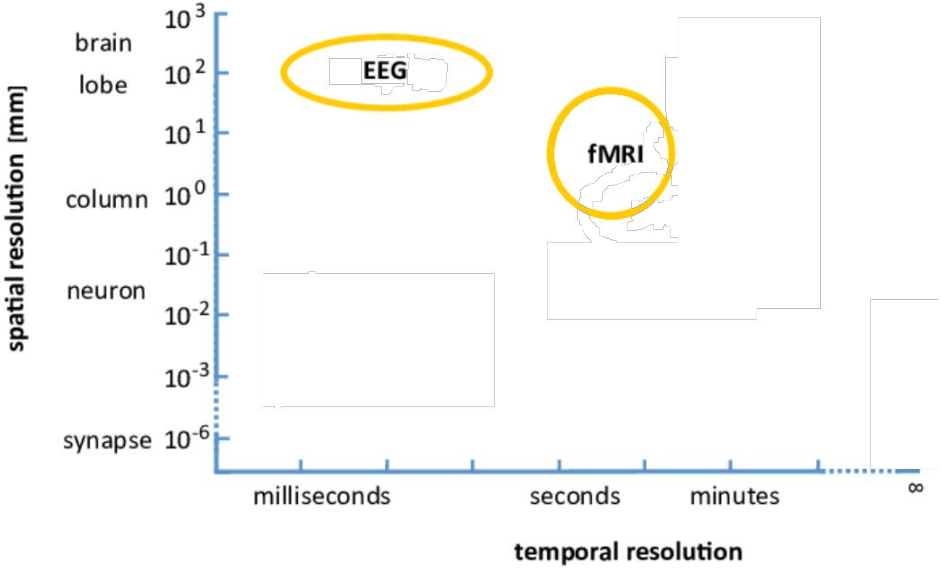




Wessel et al. (2023)

Concurrent EEG and tTIS

- EEG can capture the cortical response to tTIS
- EEG provides millisecond-level temporal resolution
- Only studies of tTIS with fMRI



Comparison between EEG and FMRI [1]

[1] Pfister et al. (2014)

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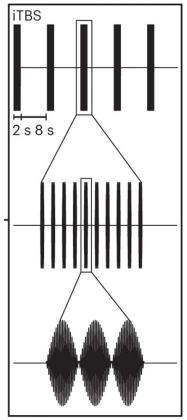
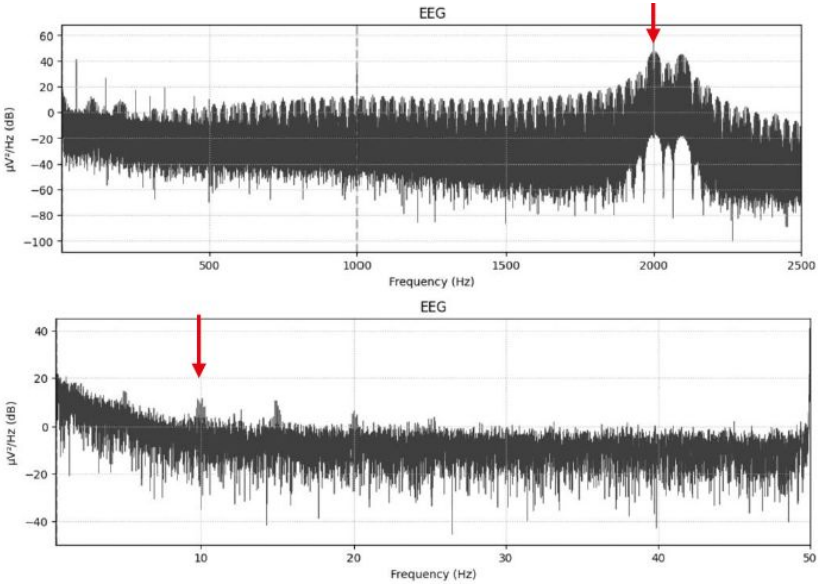
System configuration and EEG artifacts

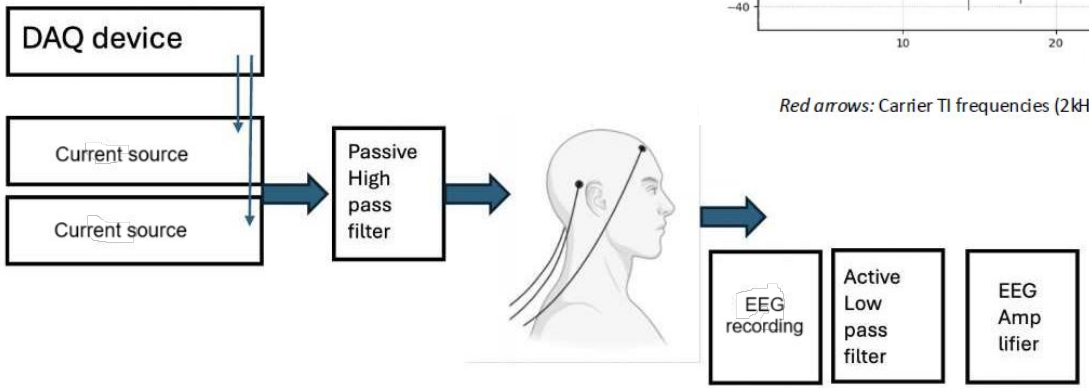


Intermittent theta burst tTIS leads to artefacts in EEG recording



Red arrows: Carrier TI frequencies (2kHz, 2.1kHz), TI stimulation artefact at 5Hz (FFT)

Solution:



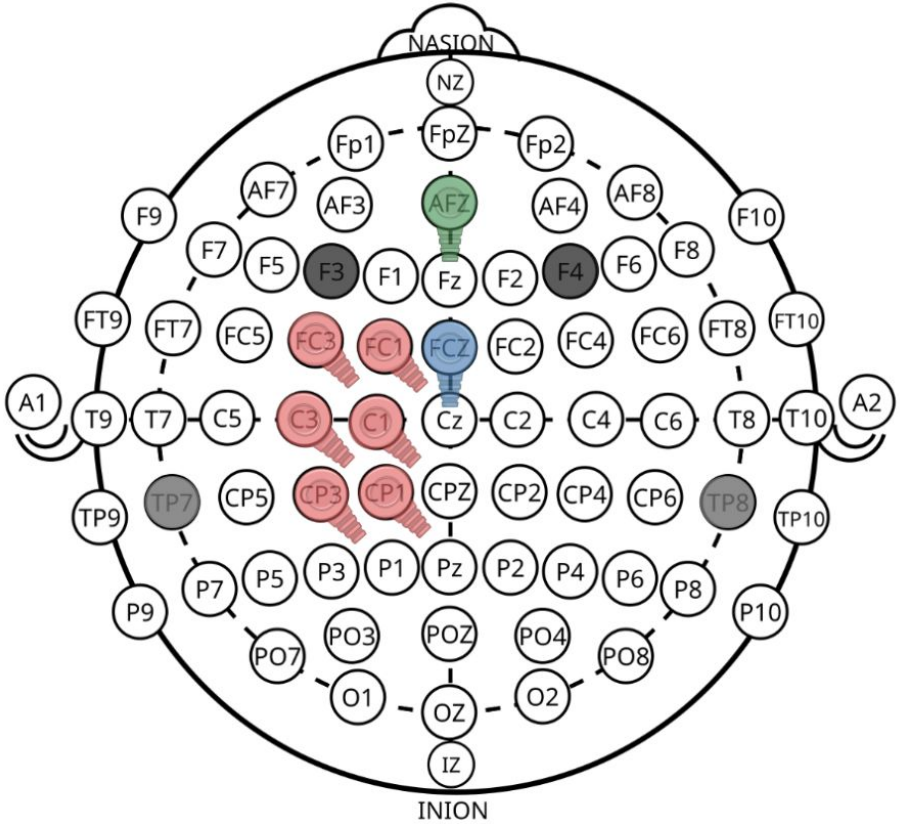
EEG and tTIS electrodes placement

EEG:
AFZ and FCZ for ground and reference electrodes, respectively

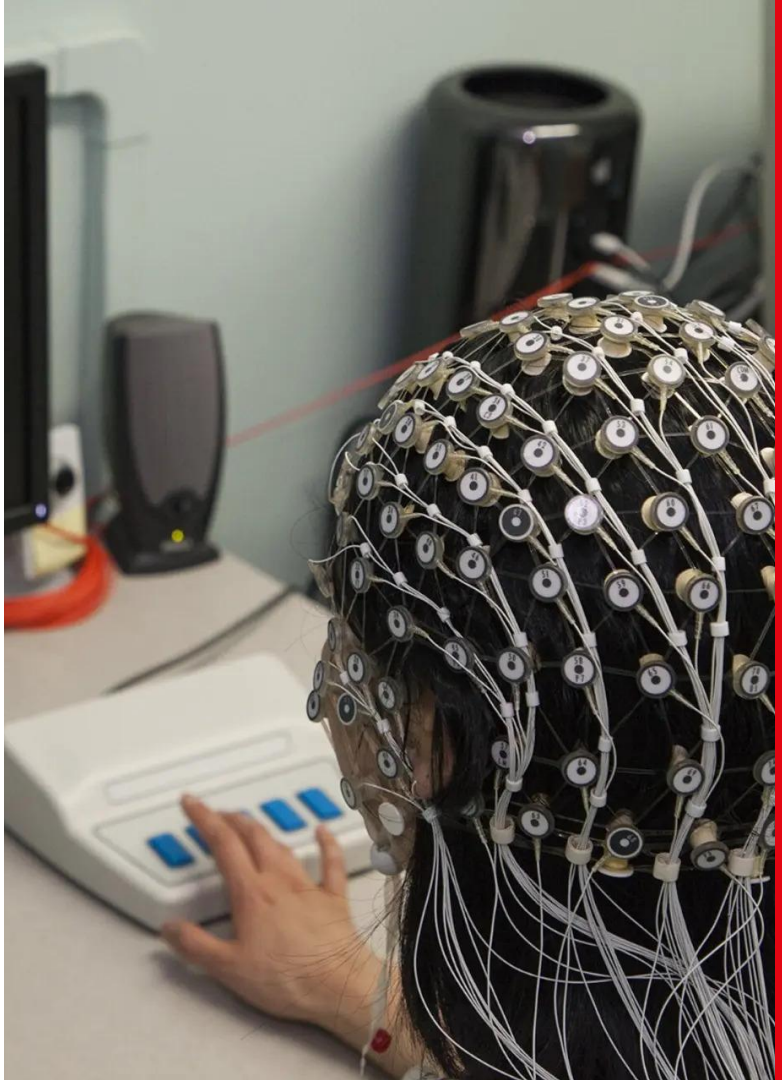
(FC1, FC3, C1, C3, CP1, CP3) for counter electrodes [1]

Right handed SRT task:
L SMC, L dPMC, L M1, L S1 [2]

tTIS:
F3, F4, TP7, TP8 [3]



[1] Dyck et al. (2024)
[2] Hardwick et al. (2013)
[3] Wessel et al. (2023)



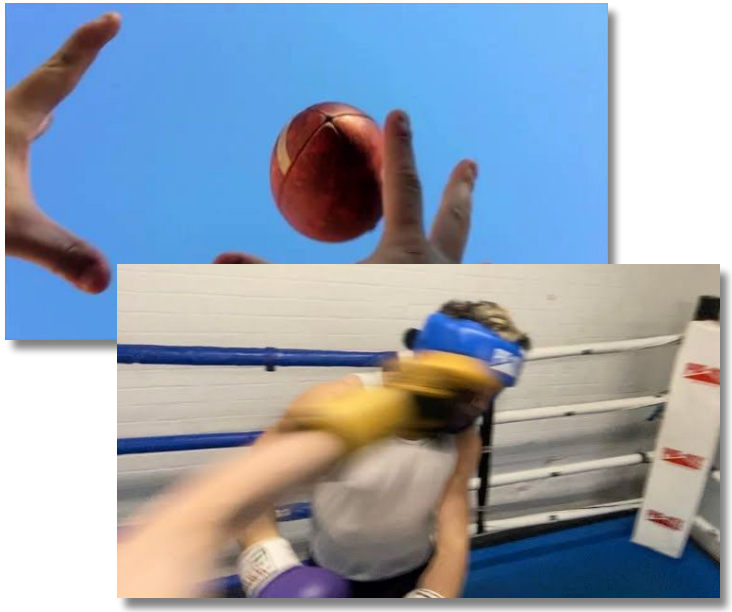
Task design

Hypothesis

Striatal involvement

Motor learning

Hypothesis



⇔

Target reaching task

- ❏ Precise reaching movement
- ❏ Reinforcement learning
- ❏ Reflex and speed

TBI related motor skill impairment can be more efficiently treated by training on pre-learned motor skills

Steward et al. (2018), Wolff et al. (2023)

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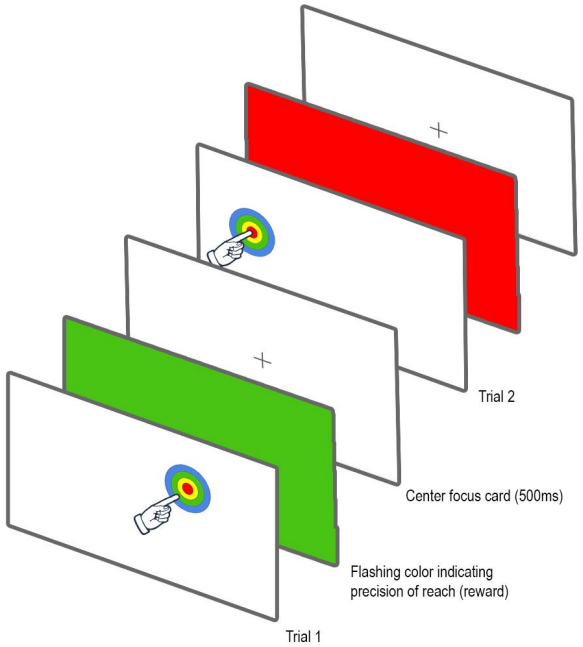
Reaching serial reaction time task



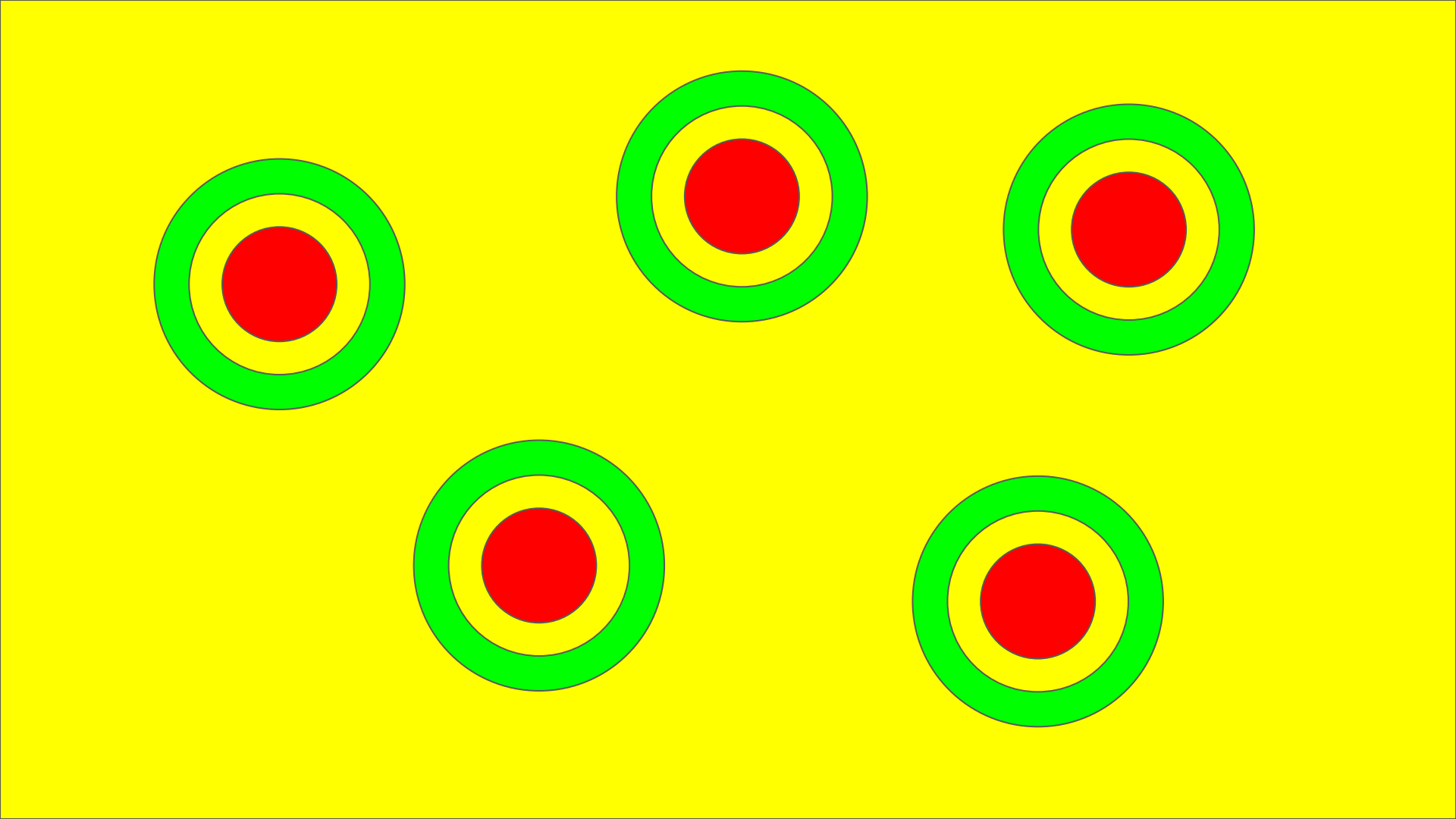
Targets apparition in hidden pattern. Next target appears after fixed time period (500 ms) . Subject returns to fixed platform between each trial.

Involves:

- ❏ Reflex and speed
- ❏ Reinforcement learning
- ❏ Implicit sequence learning

Metrics:

- ❏ Reaction time (Time between visual stimulus and response)
- ❏ Accuracy (Target accuracy)

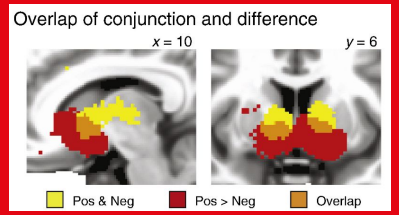


Striatal involvement during task

Reinforcement learning

Striatal BOLD response to positive and negative outcomes

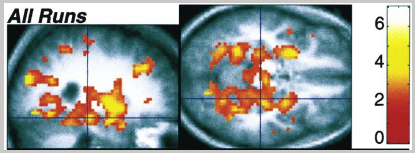
ctTIS of striatum leads to disruption of reinforcement learning



Sequence learning

Activation of Putamen and Caudate during implicit SRT tasks

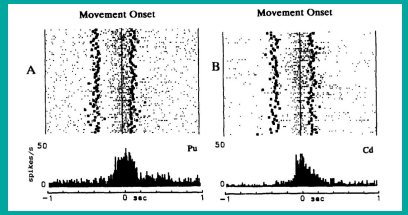
Impaired performance on implicit SRT tasks in patients with striatal dysfunction (PD, HT)



Reaching movement onset

Striatal activation at reaching movement onset in primates

Impaired performance on reaching tasks associated with striatal degeneration



Bartra et al. (2013) , Vassiliadis et al. (2024), Schendan et al. (2003), Doyon et al. (1997), Rauch et al (1997), Jaeger et al. (1995), Gooijers et al. (2016)

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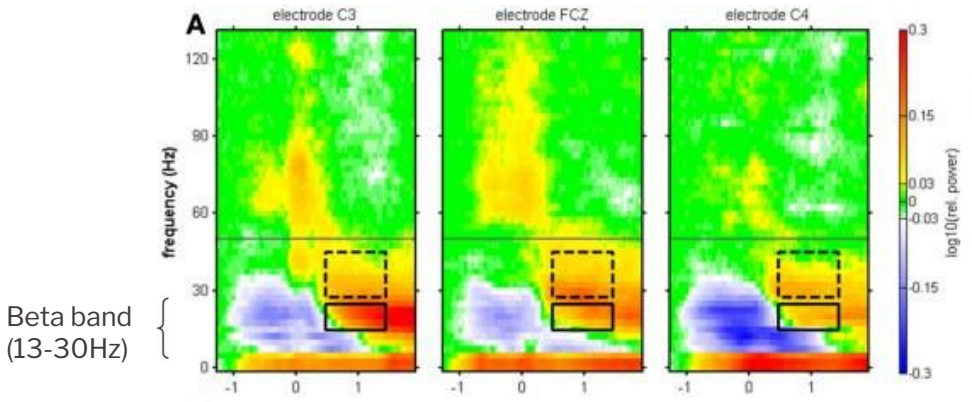
EEG and motor learning

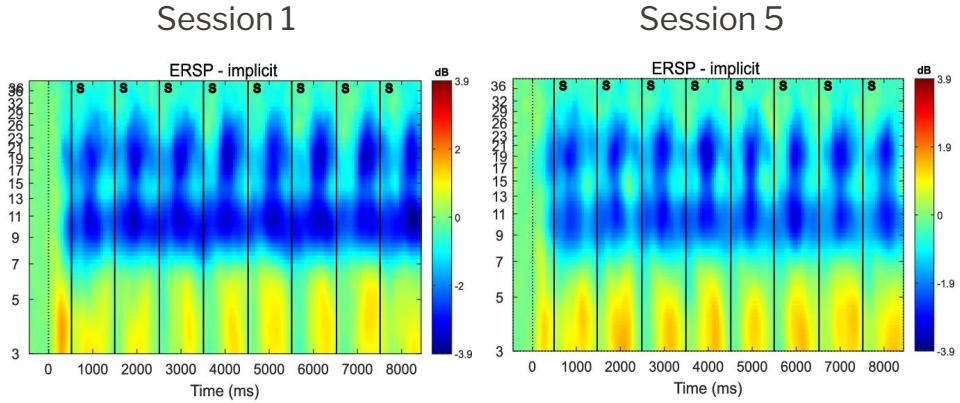
Reaching movement EEG spectrum

- Beta power suppression during movement
- Post-movement beta rebound (PMBR)

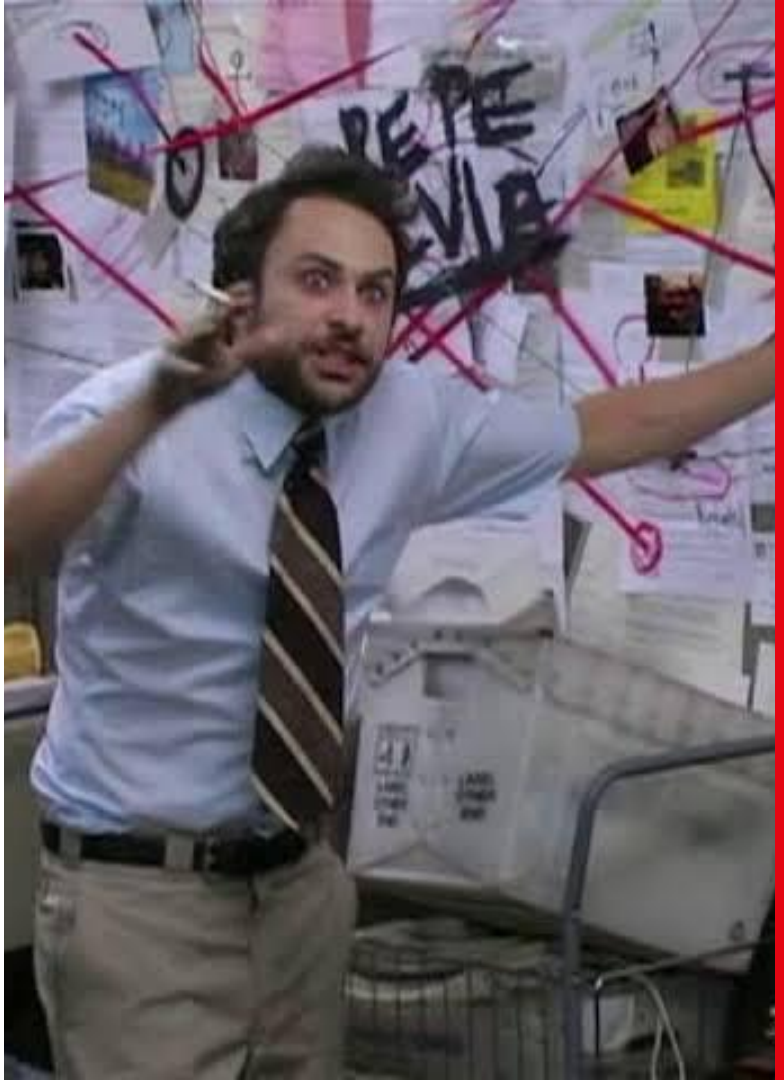


Event related spectral perturbation in SRTT

- Decreased beta band suppression
- Beta abnormalities in mTBI patients



Demandt et al. (2012)
Dyck et al. (2024)
Rier et al. (2021)



Study design

Subject selection

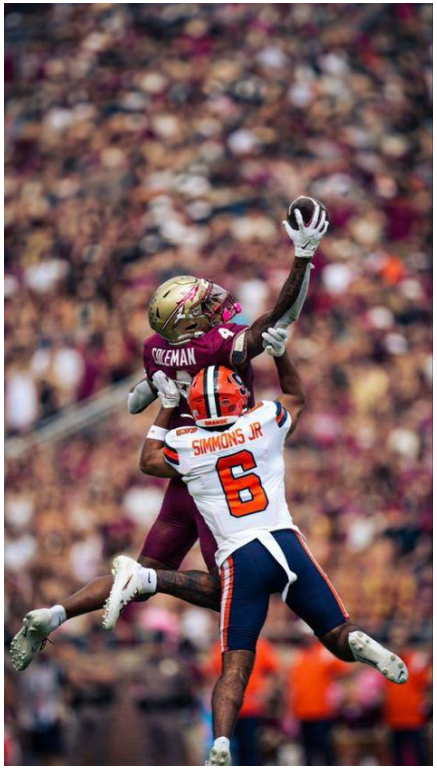
Experiment

Timeline

Subjects

Inclusion criterias

- Age range: 30yo +/- 10y
- History of multiple head impacts
- Clinical symptoms present for more than 12 months
- Cavum septum pellucidum
- Normal beta amyloid cerebrospinal fluid (CSF) levels
- Elevated CSF p-tau/tau ratio
- Negative amyloid imaging (on PET imaging)
- Positive tau imaging (on PET imaging)
- Cortical thinning/atrophy (MRI)



Exclusion criterias

- History of clinical stroke or brain tumor
- Visual or hearing impairment severe enough to compromise cognitive testing
- Current clinically significant infectious disease, endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer.

Experiment overview

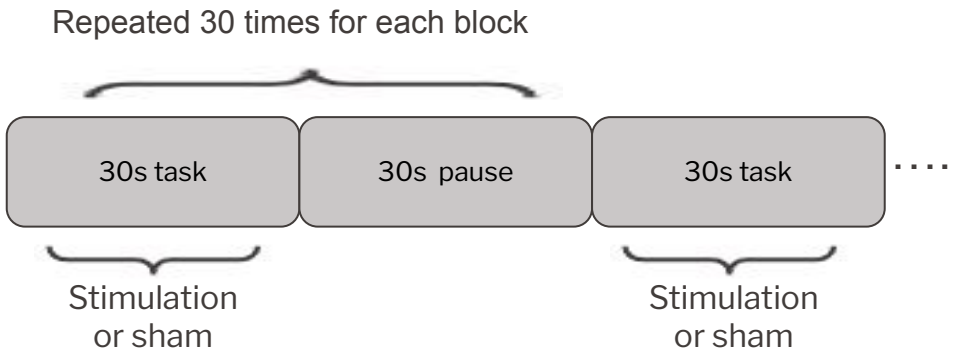
n=40 half TBI half HC

Active condition: Theta burst TI stimulation 2s every 10s

Sham condition: HF stimulation

Two conditions and two groups:

TBI + tTIS	**Healthy control + tTIS**
TBI + Sham	**Healthy control + Sham**



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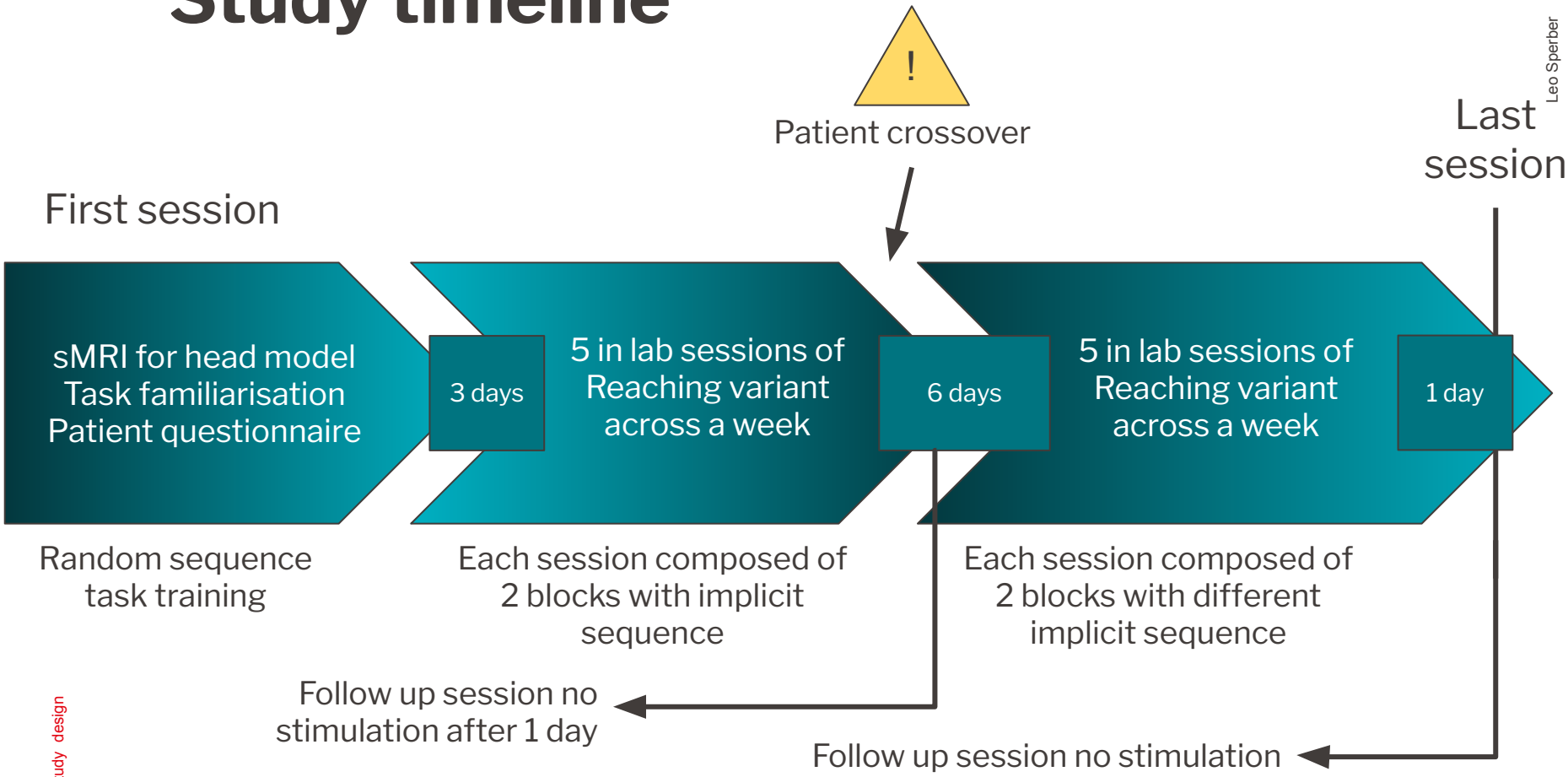
Study timeline



Discussion

Study outcome

Limitations

Other studies

Possible study outcome

More tTIS-related improvement in TBI patients than in HC
Supports hypothesis that tTIS has larger effect in populations with more pronounced brain malfunctions

tTIS of the striatum improves task performance progress
Supporting evidence of striatal involvement in task

tTIS modulates beta oscillations abnormalities in TBI patients
Lower beta power in beta suppression and post-movement beta rebound for TBI patients increased with tTIS

Limitations

Possible confounders:

History of painkiller use:
Widespread use of Ketorolac and Vicodin in NFL

Sport-specific performance:
Absence of TBI linked to played position

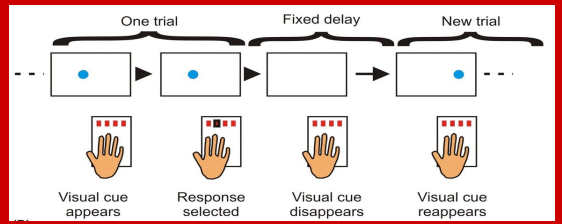
TBI expression variability:
Can affect different parts of brain depending on trauma

Principal limitation:
Innovation

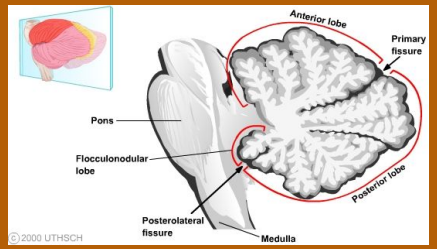
- ❏ tTIS is a novel stimulation method
- ❏ Few studies specific to ex-athletes
- ❏ New motor task
- ❏ No studies on concurrent tTIS and EEG during motor task

Research suggestions

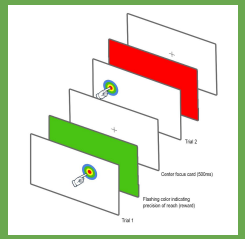
Compare task performance improvement of TBI ex-athletes with well-established SRTT



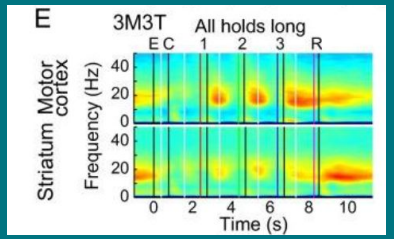
Compare motor cortex modulation with striatal tTIS vs stimulation of other brain regions

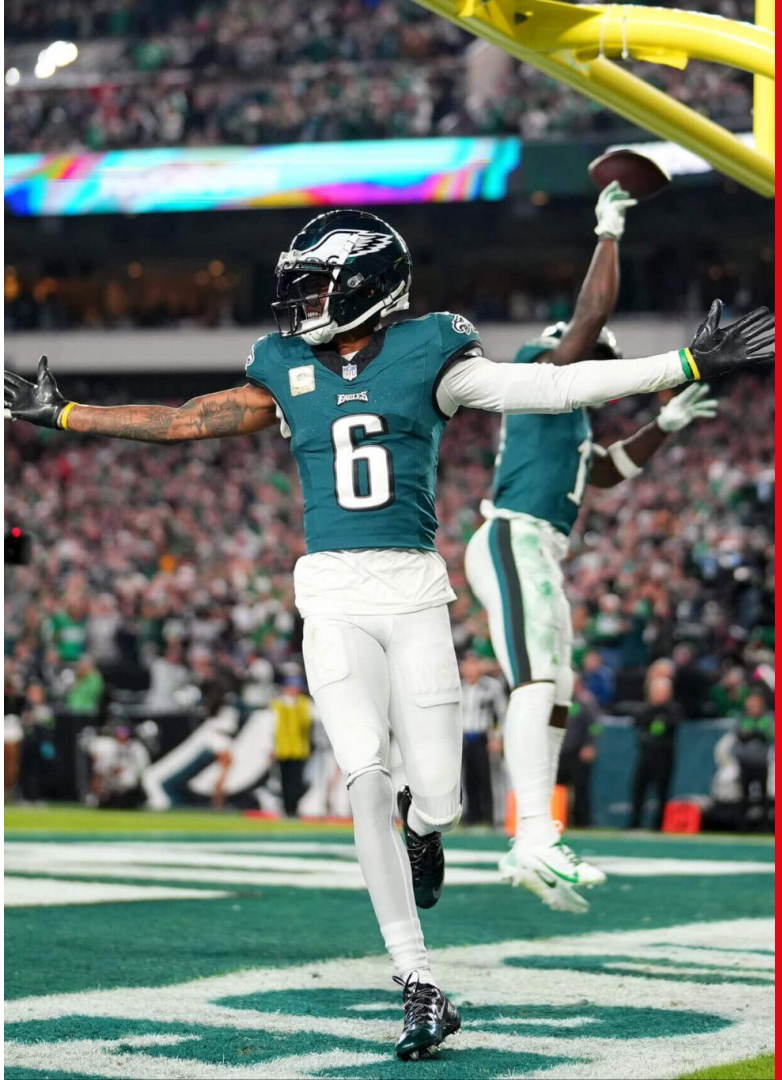


Compare motor performance in task between sports related TBI and other types of TBI



Compare task performance with different striatal tTIS patterns in healthy patients





Conclusion

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Basal ganglia and motor cortex

Problem in human studies: temporal resolution of fMRI
Solution: Primate studies with invasive electrodes

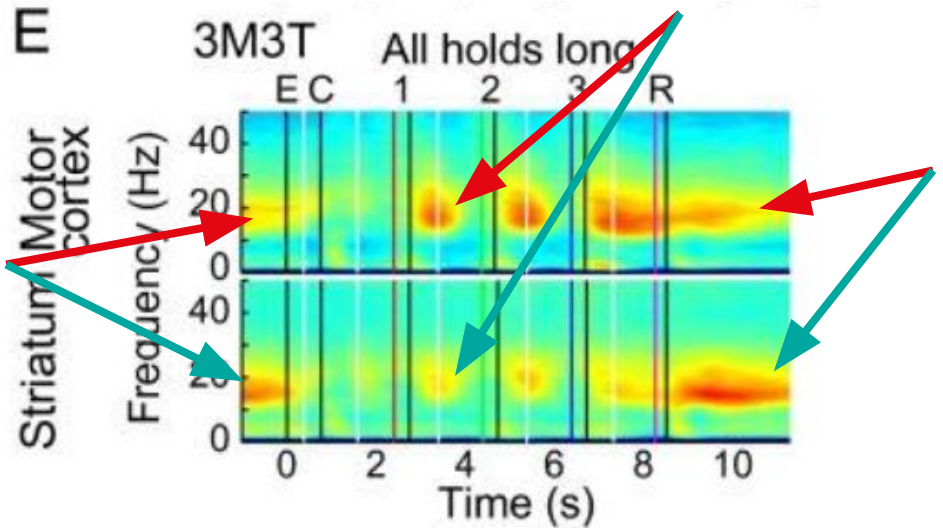
B

E: no visual stimuli
C: visual stimuli onset
1: first movement
2: second movement
3: third movement
R: Reward

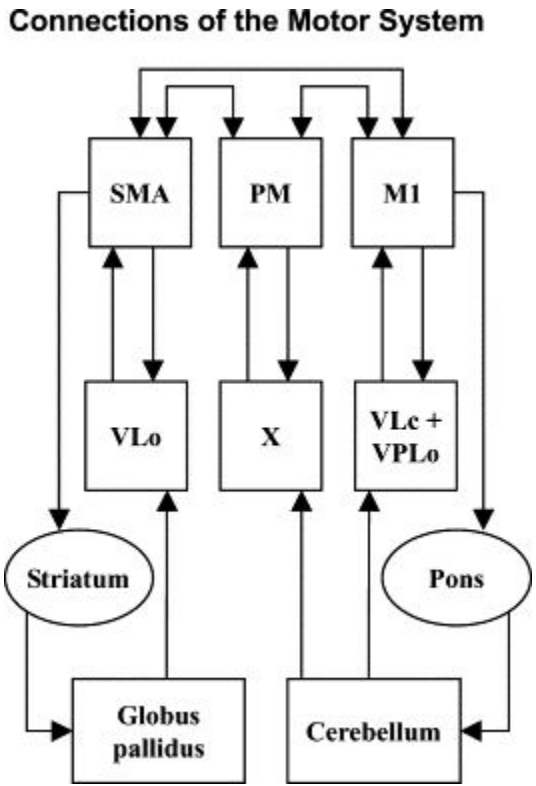
Focused state

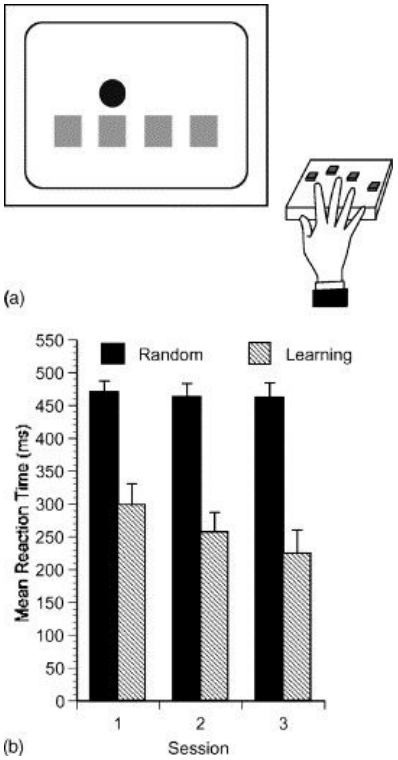
Post movement beta rebound

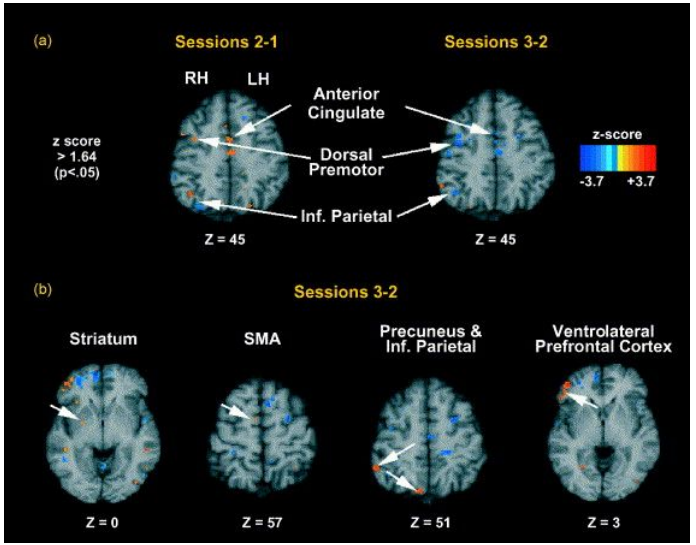
Reward



Striatal to motor cortex projection







Doyon et al (2003)