Transcranial Temporal Interference Stimulation (tTIS) for Alleviating Apathy in Parkinson's Disease Patients

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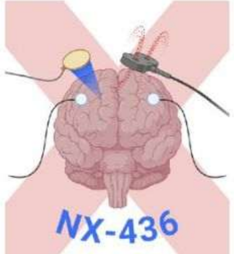
Teaching assistant: Michele Di Ponzio

Presenters: Leo Ganser, Penghui Du, Wenxin Che



Content

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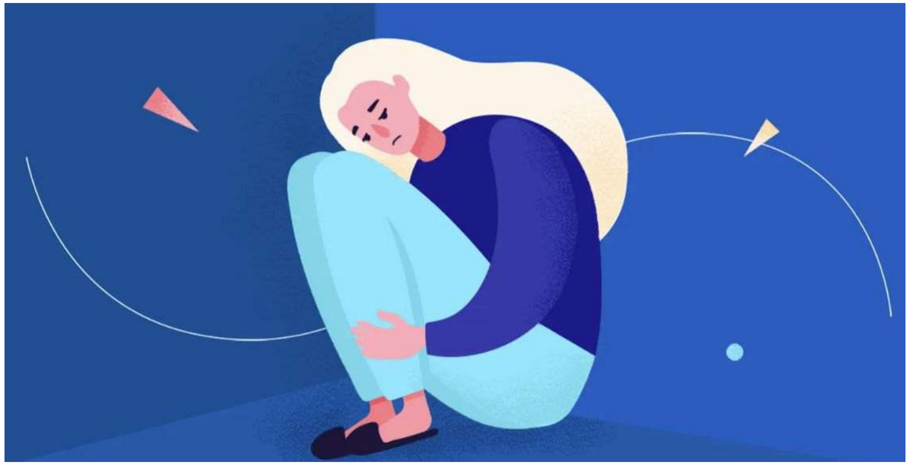
What is apathy?



https://www.calmclinic.com/anxiety/apathy

https://www.calmsage.com/what-is-apathy-causes-symptoms-treatment/

- **Definition:**

  “Medically, apathy is a lack of goal-directed activity. It also presents as a lack of interest and emotional expression.”

  —Cleveland Clinic Health Library

- **Apathy:**
  - Disengaging from work, hobbies and loved ones;
  - Lack of motivation for doing daily activities;
  - Decreased emotion expression; etc.

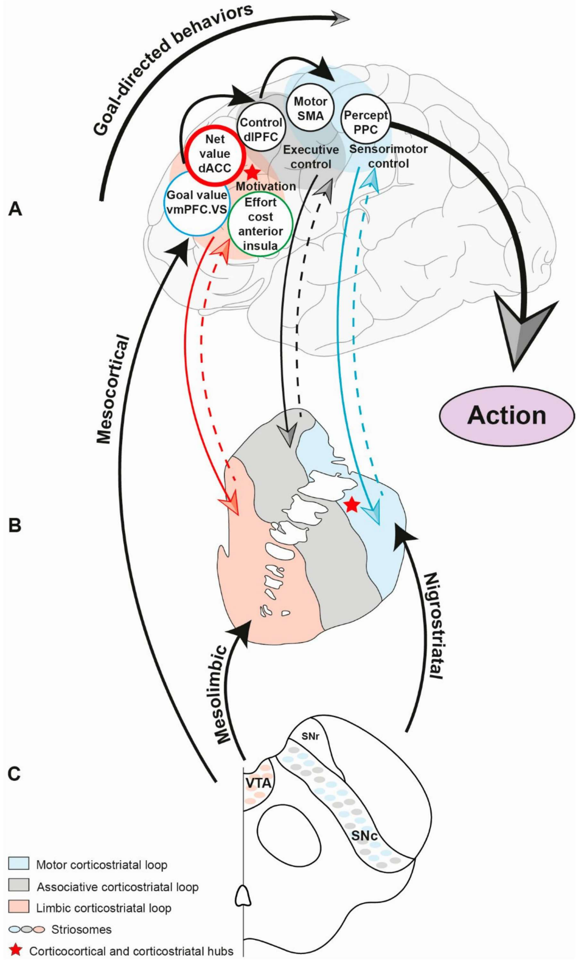
- **A transdiagnostic syndrome:** Commonly present in patients suffering from other neurological disorders.

Apathy in Parkinson's Disease (PD-Apathy)

In this project, we will be focusing on a subpopulation of apathy patients: Apathy in Parkinson's Disease (PD-Apathy).

Why PD-Apathy?

- ❖ Shared population:
  - ➢ **~40%** of PD patients also experience **apathy.**[1-2]
  - ➢ Treatments for PD could sometimes even worsen pathy.[3-4]
- ❖ Shared systems:
  - ➢ **In PD:** Dramatic loss of dopaminergic neurons[5], reduced functional connectivity in mesolimbic-striatal and cortico-striatal loops[6].
  - ➢ **In Apathy:** Strongly dependent on cortico-striatal & nigrostriatal connectivities[7-10] and decreased striatal dopamine levels[11].
- ❖ Pathophysiological interplay[12]



Circuits involved in human apathy. Figure adapted from (Bereau et al., 2023).

What is transcranial temporal interference stimulation (tTIS) ?

Reminder:

- ❖ **Two pairs** of electrodes that send **high frequencies currents**
  - ➢ Neurons **don't respond** to ~KHz stimulation
- ❖ The **overlap** of the two high frequency currents (~KHz) with Δf frequency difference creates a **lower frequency envelope (Δf)** at specific brain regions.

What are the advantages of tTIS?

- ❖ Target **deep brain structures** with good focality (vs. TMS / tDCS / tACS). [13-14]
- ❖ Non-invasive, no tissue damage (vs. DBS). [13-14]

Side note:

- ❖ **tTIS is subthreshold stimulation.**[13]

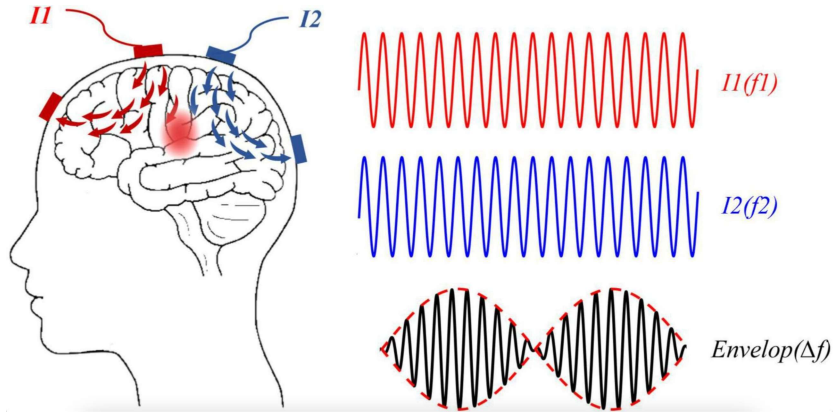


Figure adapted from (Guo W et al., 2023)

Why tTIS is promising for treating PD-Apathy?

Currently, methods for treating PD-Apathy are limited:

- ❖ Pharmacotherapies (e.g., levodopa[15], D2 / D3 agonist[16-17]):
  - ➢ **Side effects:** Withdraw rebound[15]; Dyskinesia[19] and hypotension[18].
  - ➢ **Alternative mechanisms:** Dopamine depletion alone cannot fully account for the symptoms of PD-related apathy[33].
- ❖ Brain stimulation techniques:
  - ➢ **Deep brain stimulation:** Promising in preclinical trials targeting ventral striatum (NAc) and ACC[2,21], but very invasive.
  - ➢ **Repetitive TMS**: Non-invasive, promising for improving PD-Apathy[20,22,23] via cortical stimulation, can't target deep brain structures.

tTIS offers a unique approach that enables non-invasive stimulation of deep brain structures, such as the ventral striatum, with decent focality!

https://www.news-medical.net/health/An-Overview-of-Pharmacotherapy.aspx

https://en.wikipedia.org/wiki/Transcranial_magnetic_stimulation#/media/File:Neuro-ms.png

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Why tTIS is promising for treating PD-Apathy?

This project aims to:

1. ***Address PD-Apathy by intermittent θ-burst tTIS during motivation-related tasks.***
2. ***Characterize the response profiles of tTIS by neuroimaging and behaviour assessments***

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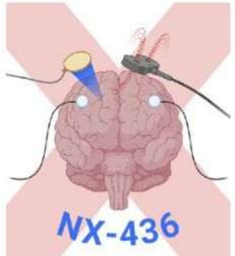

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  - ➢ What is Apathy?
  - ➢ Apathy in Parkinson's Disease (PD-Apathy)
  - ➢ What is transcranial electrical temporal interference stimulation (tTIS)?
  - ➢ Why tTIS is promising for treating PD-Apathy?
- ❖ Methods
  - ➢ Subject Recruitment
  - ➢ tTIS stimulation protocol
  - ➢ Cognitive tasks during stimulation
  - ➢ Neuroimaging and behavioural assessments
- ❖ Expected Results and Significance
- ❖ Discussion & Limitations

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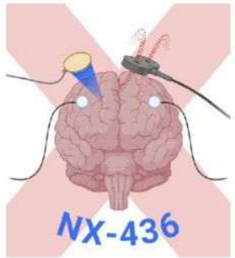
Subject Recruitment



Subjects	40 Patients
AES-C (Apathy Evaluation Scale)[26]	Apathy (above clinical cut-off)
Parkinson (UPDRS)[36]	Mild to Moderate (reasonable motor fonction)
Age	>50 years old
Medication	Dopamine based medication No DBS implanted

- ❖ Double-blind study
- ❖ **Control Group:** 20 patients receive striatum stimulation, the remaining 20 receive sham stimulation.
  - ○ **Shame** using **HF** that don't create **envelope**
- ❖ **Ethics:** All participants continue their original medication regime in the study

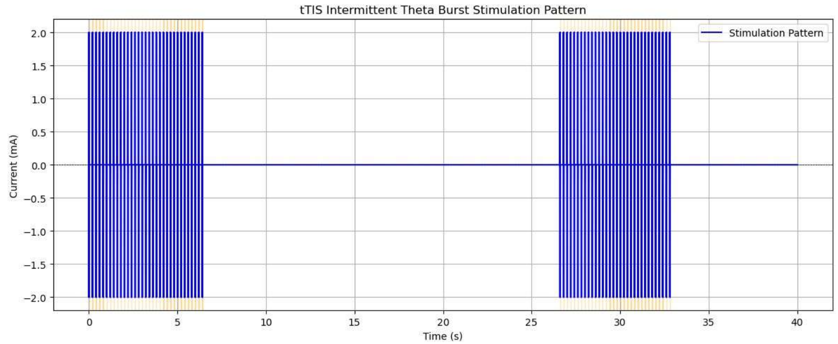
tTIS stimulation protocol

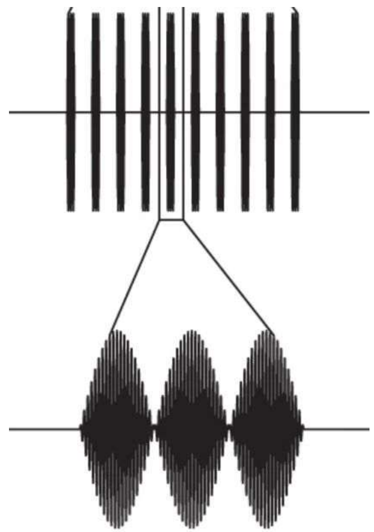
Intense stimulation protocol over 5 days

- **Why ?**
  - TMS (Stanford Neuromodulation Therapy) and tDCS => short, intensive, multi-session protocol induce long lasting changes[43] & lower relapse rates[44-46].
- 25 min/session, 3 sessions/day
- Min 30 minutes break between sessions

Stimulation setup: Using established patterns[24]:

- Electrode positions : F3–F4 and TP7–TP8
- Intermittent Theta burst stimulation(5Hz).
  - 6.5 second duration
- During burst:
  - Current : 2 mA
  - Three pulses of amplitude modulation at 100 Hz
  - 200 ms between bursts
- **Safe and tolerable:** Proven in tTIS[37-38] and tDCS studies using similar set-up[44-46]





Cognitive tasks during stimulation

- **Task** enhance **tTIS's** ability to modulate relevant circuits.
- Effort-based decision-making task
  - Has been designed for a study for PD patients[3]

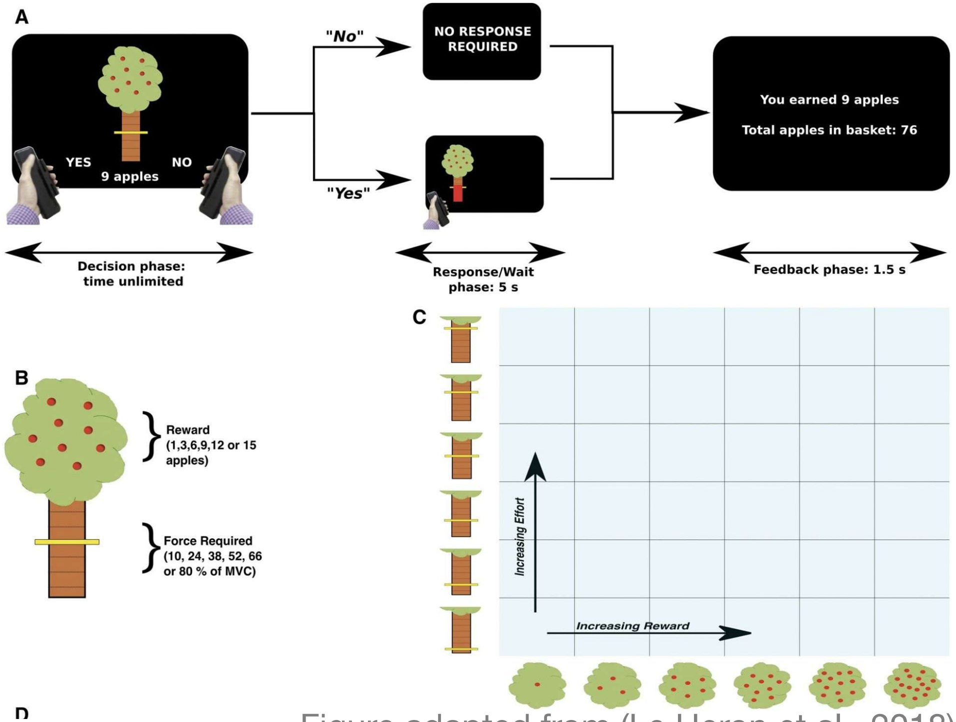
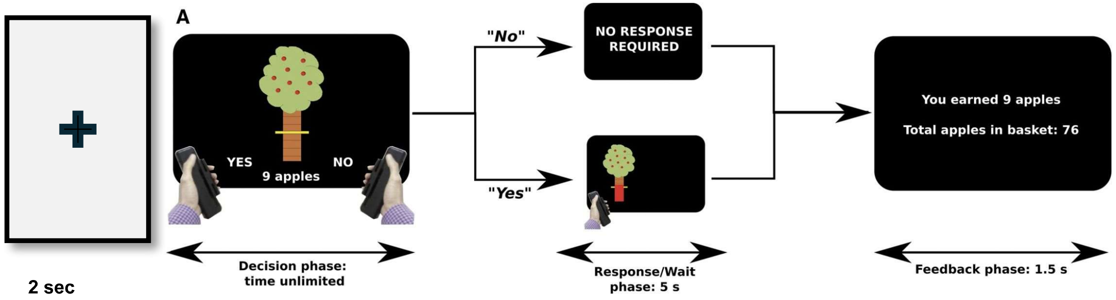
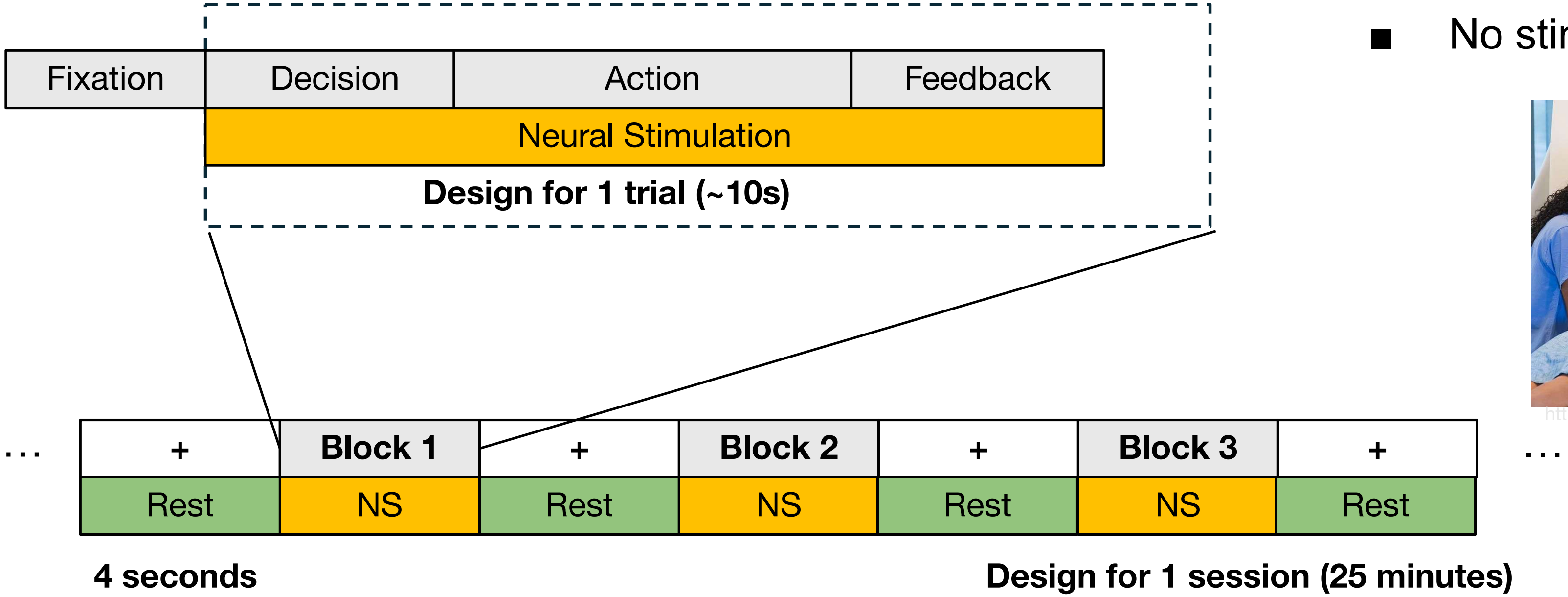


Figure adapted from (Le Heron et al., 2018)

Experimental design



- **Task-based FMRI** during **first** and **last** session of the therapy
  - ➢ To observe progression and validate the therapy
    - ■ No stimulation during fmri



https://www.prevea.com/resources/mri

Neuroimaging and behaviour assessments

- **Disease evaluations (Clinical diagnostic scales)**
  - **Rationale:**
    - **Short-term effect:** To assess if the acceptance during the trial are improved after the stimulation.
    - **Long-term effect:** To assess if the apathy scores decrease while acceptance improved after the stimulation.
  - **Metrics:**
    - AES-C[26] / LARS[41], assess severity of apathy from behavioural, emotional and cognitive aspects.
    - UPDRS[36], control for the influence of Parkinson's Disease.

- **Task-based fMRI connectivity**
  - **Rationale:**
    - PD-Apathy patients show **reduced connectivity** between ventral striatum and ACC, OFC, etc[7,8,9,40].
    - Measure whether task-state connectivity is strengthened after tTIS treatment[14,25].
  - **Metrics:**
    - Seed-based functional connectivity (FC, calculated by Pearson Correlation).
    - Seed-based effective connectivity (EC, calculated by Granger Causality Analysis).
    - Focus on NAc (ventral striatum) to cortical motivational circuits (ACC, OFC, vmPFC, etc.)

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Neuroimaging and behaviour assessments

- **Resting state fMRI (rs-fMRI) connectivity and activities**
  - **Rationale:**
    - rs-fMRI FC indicate **strength of cortico-striatal projections**, also super relevant to PD-Apathy[9,40].
    - PD-Apathy patients show **reduced fMRI activity** in some regions (e.g., ACC)[10,15,40],
  - **Evaluation metrics:**
    - Seed-based rs-fMRI FC;
    - Seed-based rs-fMRI EC;
    - Changes in activity-based metrics such as ALFF[27,40] and ReHo[28].

- **MRS: Changes in metabolite concentrations**
  - **Rationale:**
    - Apathy is correlated with altered metabolite concentrations (e.g., lower NAA/Cr ratios in ACC[29,32]).
  - **Evaluation metrics:**
    - Use MRS to quantify metabolites in ACC[29,32] and other cortical regions.

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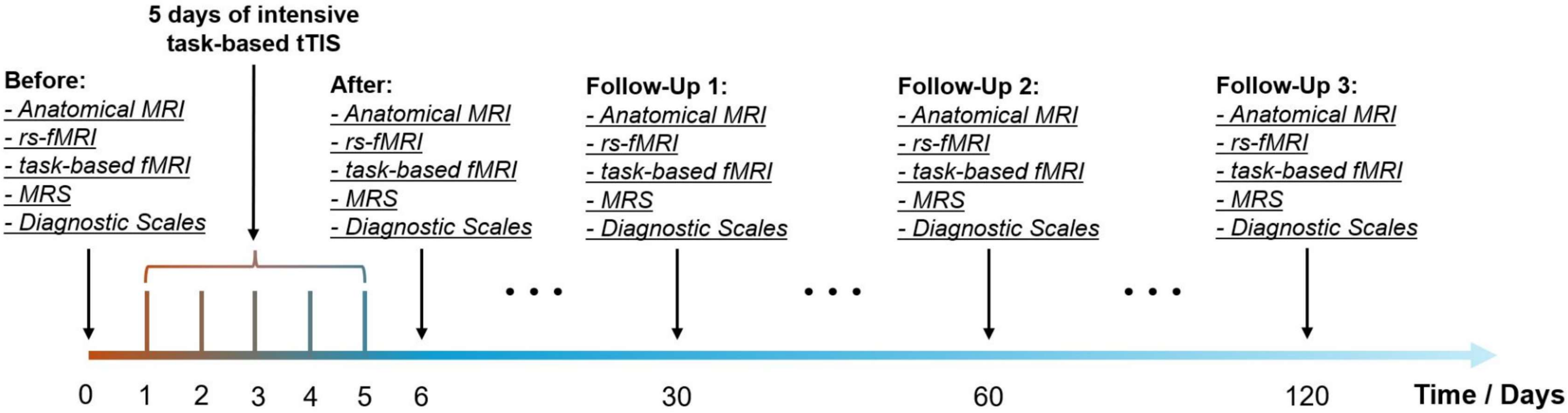
Neuroimaging and behaviour assessments



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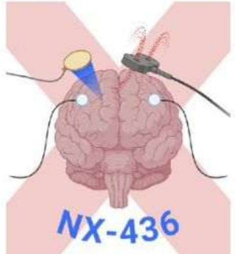
Expected Results & Significance



❖ Effects compared to sham experiment

- ➢ **Behavioral Changes:** Significant and persistent **increase in acceptance rate** to low-effort, low-reward proposals vs. sham group.
- ➢ **Functional Changes:** Persistently **strengthened striatal-cortical FC / EC** vs. sham group.
- ➢ **Metabolite Changes:** Significant and persistent **increase in NAA/Cr ratio of ACC**.
- ➢ **Apathy Scores:** A significant **reduction in apathy severity**. i.e. Significant and persistent **decrease in LARS and AES-C**, with larger scores indicating more severe apathy (LARS: cutoff=-15; AES-C: cutoff=40)
- ➢ **Minimum influence from PD:** *No significant variation* observed in *UPDRS scores* vs. sham group.

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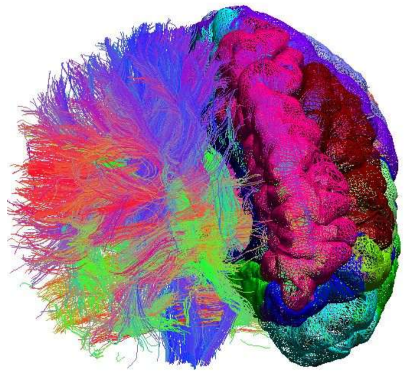
Expected Results & Significance

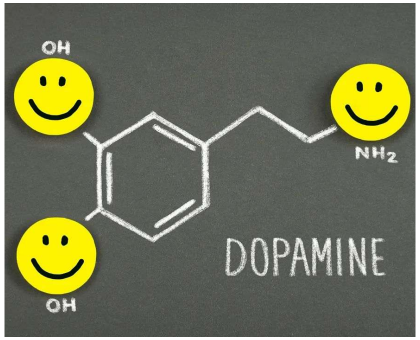
❖ **Clinical Significance:** A non-invasive technology for treating apathy (if working well), together with in-depth evaluation of its mechanism.

❖ **Scientific Significance:** Causal understanding of how cortico-striatal connectivity and the striatal dopamine system regulate motivated behaviors (not super clear yet); Benefit other research involving motivation system.



Strengthened striatal-cortical connectivity

Improvements in motivated behaviours



Deepen current understanding of motivational circuits

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Discussion and Limitations

- Will we be able to introduce long-term neuroplasticity?
  - No tTIS protocol had successfully induce lasting changes before.
  - Proven possible for other suprathreshold techniques (e.g., TMS[42])
- Is stanford neuromodulation therapy (TMS) transferrable to tTIS?
- Other possible task designs. (e.g., 2 choices instead of multiple: high-effort high-reward vs. low-effort low-reward)
- More routine sessions? => Drop out / Worsen performance.
- More intensive protocols e.g., SNT? (Safety, tolerability, and side-effects => need further investigation)
- (If therapy works well,) Is it possible to generalize to other apathy patients? (e.g., AD-Apathy, Depression-Apathy)

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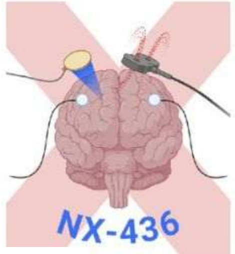

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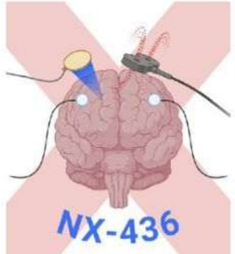

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Thank you for your attention!

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