



**Laidlaw Scholars Undergraduate Leadership and Research
Programme**

Research Proposal

**Clinical Outcomes Following Transcranial Direct
Current Stimulation (tDCS) for Neuropsychiatric
Symptoms (NPS) in Alzheimer's Disease**

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I. Introduction

Global dementia cases are projected to triple by 2050, with an estimated 153 million people living with dementia worldwide¹. Alzheimer's disease (AD), the most common form of dementia, affects far more than those diagnosed, influencing patients, families, friends, and broader society through profound emotional, social, and economic consequences².

I have long been fascinated by how the brain works, but over the past year, my interest has deepened into questions of what happens when the brain does not function properly. What differentiates neurodegeneration from normal aging? Why does Alzheimer's disease occur, and why does it present so differently across individuals?

As an aspiring neuroscientist, I recognise that dementia and Alzheimer's disease will define the era of medicine and neuroscience in which I hope to work. I wish to dedicate my career to better understanding the complexities of neurodegeneration and Alzheimer's disease, and I see no better way to begin this journey than as a Laidlaw Scholar working on this topic.

Working under the supervision of Dr Sanjeev Kumar, I will study the clinical effects of transcranial direct current stimulation (tDCS) on neuropsychiatric symptoms (NPS) in individuals with Alzheimer's disease. Studying the effect of tDCS on NPS is important because neuropsychiatric symptoms of dementia, such as agitation and aggression, represent some of the most challenging and distressing aspects of AD for patients, caregivers, and healthcare systems³. To prepare for 2050, we need to find ways to mitigate and address these symptoms, ultimately improving patient outcomes and burdens on the healthcare system.

This study provides a unique opportunity to examine whether tDCS can meaningfully improve NPS in individuals with AD. Through this project, I aim to develop a strong foundation in clinical research by statistically analysing validated measures of NPS and evaluating the clinical relevance of this emerging treatment.

I. Research Objectives & Questions

Primary Objective:

- Evaluate the effect of transcranial direct current stimulation (tDCS) on overall neuropsychiatric symptom (NPS) burden in individuals with Alzheimer's disease, as measured by total Neuropsychiatric Inventory (NPI) scores, compared to sham stimulation.

Specific Objectives:

- Perform a brief literature review on the ongoing state of tDCS for the treatment of NPS in Alzheimer's Disease

- Identify literature focusing on specific NPS defined by NPI
- Review the accuracy of NPI as a measure of NPS for Alzheimer's
- Determine which statistical tests to use for later analysis based on established standards in the literature
- Determine which specific NPI symptom subscales show the greatest improvement following active tDCS.
 - The following NPS will be examined: Delusions, Hallucinations, Agitation/Aggression, Depression/Dysphoria, Anxiety, Euphoria/Elation, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant motor behaviour, Sleep and nighttime behaviour disturbances, Appetite and eating abnormalities
- Conduct further analysis on specific subscales which demonstrate the greatest improvement
- Assess whether changes in overall and subscale NPS are sustained from two weeks to four weeks post-intervention.
 - Complete this analysis for all subscales and overall symptoms
- Explore whether baseline severity of overall NPS or specific symptom domains is associated with the magnitude of response to tDCS.
- Does demographic data influence the effect tDCS has on patients?
 - Examine the influence of sex, age, ethnicity, disease progression, etc

Research Questions:

1. Does active tDCS lead to greater improvement in overall neuropsychiatric symptoms compared to sham stimulation, as measured by total NPI scores?
2. Which NPI symptom subscales demonstrate the greatest responsiveness to tDCS?
3. Are improvements in overall and subscales specific to NPS observed at two weeks maintained at four weeks following the intervention?
4. How does baseline severity of NPSs influence the success of tDCS? In which type of patients are the effects most or least pronounced?

I. Methodology

Descriptive statistics will be used to summarise participant demographics and baseline clinical characteristics. Changes in NPI total and subscale scores across assessment time points (baseline, post-intervention, and follow-up) will be analysed using linear mixed-effects models or repeated-measures ANOVA, with time and treatment group (active vs. sham tDCS) included as fixed effects. Time-by-treatment interactions will be used to assess treatment effects. Effect sizes will be calculated to estimate the magnitude of observed changes.

Pre-Laidlaw: Literature review, develop familiarity with the original tTED study protocol, practice statistical analysis, and preparatory meetings with supervisors

Week 1: Finish literature review, explore datasets and descriptive analysis of demographics and baseline NPS

Week 2: Data cleaning, management of missing data, and computation of change scores

Week 3: Conduct primary analyses examining changes in NPI total scores following tDCS; calculate effect sizes, visualise symptom trajectories over time, and review preliminary results

Week 4: Analyse NPI subscale outcomes and assess maintenance of effects at short-term follow-up, examine EEG data to further validate results

Week 5: Conduct an analysis examining baseline symptom severity and treatment response; generate visual summaries of subscale-specific findings. Investigate the influence of demographic factors

Week 6: Buffer room to complete any remaining analysis; synthesis of findings, evaluation of limitations, and preparation of a final report and presentation

No travel is required beyond routine commuting to CAMH and a potential conference

I. Ethics Review

This project involves secondary analysis of de-identified data from the CAMH's REB-approved tTED study. No direct participant contact or identifiable data will be involved, and all analyses will be conducted under the supervision of the approved study investigators. My supervisor has advised me that I do not require any additional approval to conduct my project.

II. Interdisciplinary and International Focus

This research is interdisciplinary, integrating neuroscience, clinical medicine, psychiatry, and statistics to address a pressing neurodegenerative disease. By analysing clinical outcome measures following tDCS, the project bridges basic neuroscience with real-world clinical application.

Alzheimer's disease is a global public health challenge, with rapidly increasing prevalence worldwide. By 2050, 71% of people with AD will be living in low or middle-income countries⁴. Healthcare systems in many of these countries are already overburdened and will not be able to handle the growing prevalence of AD, making research into AD treatment vital for global health infrastructure.

Findings from this research may inform non-pharmacological treatment approaches that are scalable, cost-effective, and applicable across diverse healthcare systems, giving the project strong international relevance. By contributing to evidence on tDCS as a potential intervention for NPS in Alzheimer's disease, this research addresses a condition that affects patients and caregivers across cultures and national borders.

III. Outcomes

This project aims to contribute to the growing literature on non-invasive brain stimulation for neuropsychiatric symptoms of Alzheimer's disease. By evaluating the clinical impact of tDCS on NPS, the research may help clarify its role as a safer alternative or complement to pharmacological treatments.

Improving management of NPS has the potential to enhance patient quality of life, reduce caregiver burden, and alleviate strain on healthcare systems as dementia prevalence continues to rise.

IV. Research Supervisor Role

My supervisor will provide guidance on study design, statistical analysis, and interpretation of findings through weekly meetings and informal conversations in the lab. The research will be conducted within the tTED study framework at CAMH, which provides all necessary data access, computing resources, and software.

V. References

1. Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., ... Murray, C. J. L. (2022). *Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019*. *The Lancet Public Health*, 7(2), e105–e125.

2. *Alzheimer's and dementia: What's the difference?* (n.d.). Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/expert-answers/alzheimers-and-dementia-whats-the-difference/faq-20396861>

3. Cloak, N., Schoo, C., & Khalili, Y. A. (2024, February 27). *Behavioral and psychological symptoms in dementia*. StatPearls - NCBI Bookshelf. <https://www.ncbi.nlm.nih.gov/books/NBK551552/>

4. *ADI - Dementia statistics*. (n.d.). ADI - Dementia Statistics. <https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/>