Research Plan 2019-2020

Title: Auricular Vagal Nerve Stimulation in Brain and Gastric Outcomes in Functional Dyspepsia Patients
Category: Translational Sciences
Student Researcher: Isabelle Garcia-Fischer

1) The Research Plan/Project Summary should include the following:
    a) **RATIONALE:** Include a brief synopsis of the background that supports your research problem and explain why this research is important and if applicable, explain any societal impact of your research.

        i) Motor abnormalities have not been consistently shown in FD but are still believed to play an important role in the pathogenesis of symptoms. Delayed gastric emptying can be seen in 20-60% of patients.

        ii) One to two thirds of patients may have impaired slow wave propagation and abnormalities on electrogastrography (EGG). Gastric accommodation is consistently impaired in 40% of patients, which may lead to preferential accumulation of food in the distal stomach.

        iii) FD remains a common GI disorder, estimated to affect 20% of the population, and costing more than $8 billion in health care expenditures in the U.S.

        iv) Although delayed gastric emptying might be a distinguishing feature for gastroparesis, a number of patients with FD have been reported to have delayed gastric emptying. Abdominal pain/discomfort typically is the predominant symptom in functional dyspepsia.

        v) The approach taken by this study will combine brain and gut MRI in order to begin teasing apart differences in brain-gut axis (BGA) functioning between FD patients and healthy controls. The comprehensive imaging techniques will also further determine the efficacy of tVNS (eRAVANS) to differentially alleviate symptoms and normalize the BGA in these patient populations.

b) **RESEARCH QUESTION(S), HYPOTHESIS(ES), ENGINEERING GOAL(S), EXPECTED OUTCOMES:** How is this based on the rationale described above?

- **Research Question**: Will the use of active transcutaneous vagal nerve stimulation (tVNS) alter the autonomic system to attenuate symptoms associated with FD?
- **Hypotheses**:
  - ★ I conducted data analysis to test the following hypotheses that I developed:
    - Active versus inactive transcutaneous vagal nerve stimulation will increase parasympathetic nervous system activity to "meet" sympathetic nervous system activity so that symptoms will be attenuated since FD patients have an increased sympathetic nervous system
    - With the application of tVNS, high frequency (HF) power will be increased by active tVNS relative to sham tVNS
    - FD patients will consume less Ensure during the nutrient drink test (NDT)
    - Aversive symptoms during the NDT will be attenuated by active tVNS

b) Describe the following in detail:

i) **Procedures:** Detail all procedures and experimental design including methods for data collection. Describe only your project. Do not include work done by mentor or others.

- All anonymous and de-identified data used will come from pre-existing patient trials conducted for the respective research study. Each trial will have consisted of a nutrient drink test (NDT) where subjects were instructed to drink as much Ensure as possible until they reached max fullness. Every five minutes, subjects will be asked to mark the severity of the five major symptoms associated with FD (early satiation, bloating, abdominal pain, belching, nausea) on a 100 mm. line. As the NDT is being conducted, autonomic data will be collected and recorded.
- Methods Included the Use of:
  - Excel
  - Kubios
  - Matlab
  - R
  - Non-parametric T-tests
  - Two-way ANOVAS

            - Wilcoxon Rank Sum Tests
            - Kruskal Wallace Tests

    - As the student, my role will be to analyze the behavioral visits data, which will include the questionnaires, tVNS, NDT, and autonomic data.
    - Using the pre-existing data, I will run the following statistical analyses:
        - To determine if there is a positive effect using active tVNS relative to sham tVNS during the NDT (patients with FD vs. healthy control (HC)):
            - Two-way ANOVA
        - To compare HC and FD of Heart Rate Variability (HRV) data, first 6 minutes versus last 6 minutes of NDT sham versus active:
            - Non-parametric t-test
        - To compare FD vs. HC of the 6 Questionnaires (described below) :
            - Rank Sum
            - Kruskal Wallace

- I will not be interacting with patients directly, I will only be working with anonymous and de-identified data provided with the permission of the lab. The following bullet points outline the different main components of the research study. Data collected by the lab is from the following procedures:

These data were previously collected by the lab and will be provided to the student researcher:

- Nutrient Drink Test (NDT) → subjects will be instructed to drink as much Ensure as possible until they reach their MAX fullness. Throughout the NDT, a Visual Analog Scale (VAS) will be given to the subjects every 5 minutes which will ask the patients to rate their symptoms of belching, bloating, nausea, abdominal pain, and early satiation on a 100 mm. Line.
- Questionnaires → Brief Pain Inventory, PROMIS-Anxiety, PROMIS-Depression, Short Nepean, Multidimensional Assessment of Interoceptive Awareness (MAIA), PAGI-SYM. These questionnaires will be given to subjects to assess how symptoms (or lack thereof for healthy controls (HC)) affect their quality of life and mood
- Transcutaneous Vagal Nerve Stimulation (tVNS) → non-invasive tVNS will be applied to the left ear on the cymba conchae because this has been seen as the best location that is non-invasive to activate the vagus nerve.
- Autonomic data collection → autonomic data, specifically heart rate variability (HRV) data, will be collected to determine if parasympathetic activity increases instead of sympathetic activity being heightened and thus, a decrease in symptoms could occur. Specifically, respiration, ECG, and EEG were monitored.

“Role of Student” and “Role of Mentor”
Make bullets in this section to describe specifically what you worked on/contributed to and what your mentor(s) worked on/contributed to related to your project.

Role of Student Researcher	Role of Mentor
Literature review Development of hypotheses Data Analysis: ● Data preparation and cleaning ● Digitizing questionnaires ● Annotating physiological recordings of respiration and heart rate ● Using Excel, Matlab, R, and Kubios to analyze the autonomic data (which includes ECG data), NDT, and VAS Evaluation of data Research paper creation Consulting with mentor and lab members	Data Collection: ● Screening and questionnaires directly with patients ● Conducting inactive and active tVNS ● Administering nutrient drink test Providing guidance for student researcher during the research process

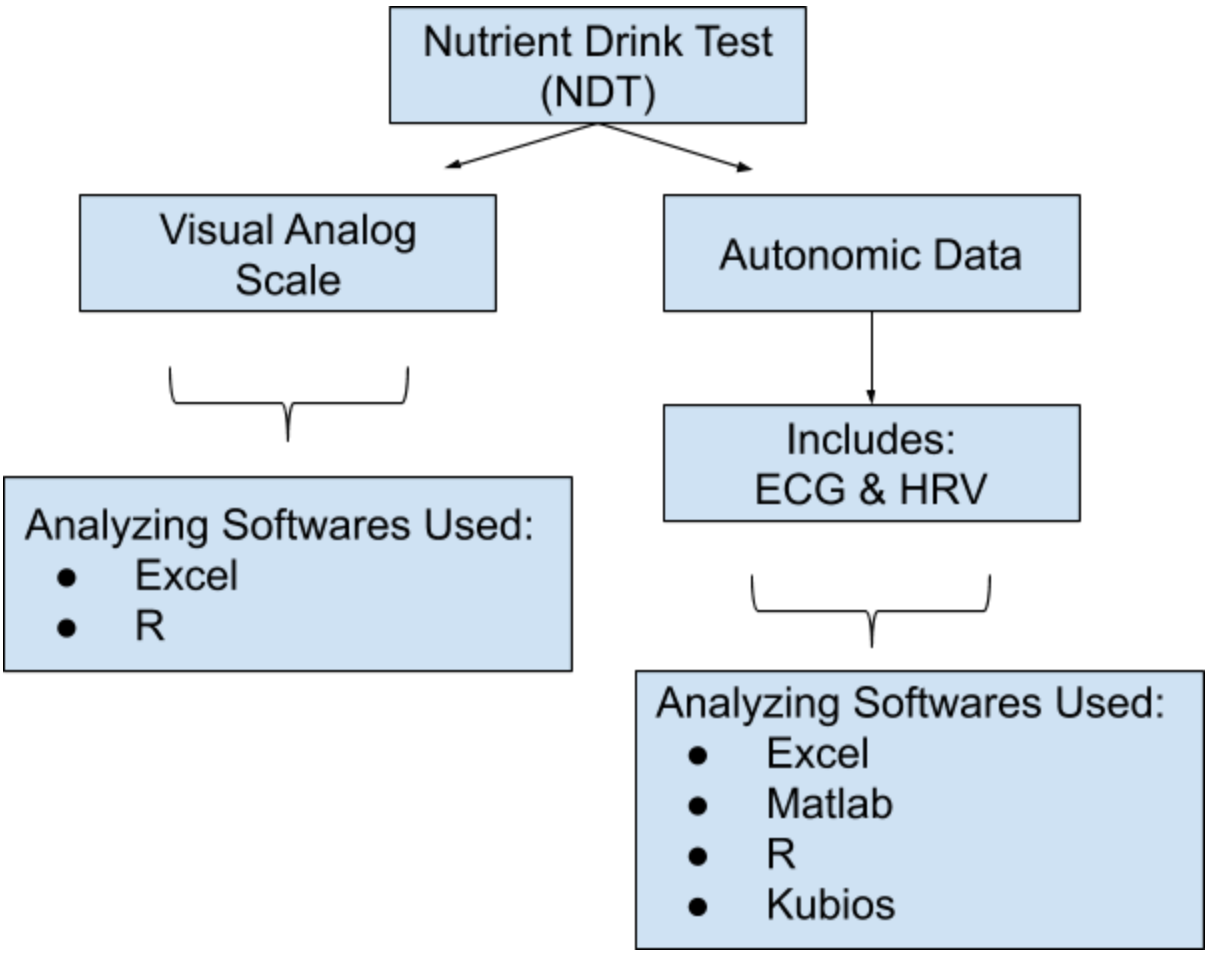

Figure: The different components that comprised the NDT and the respective statistical tests that will be run for each component. (Source: Student Researcher)

ii) **Risk and Safety**: Identify any potential risks and safety precautions needed.

- All patient information is confidential and will not be discussed outside of the medical team I will be working with
- All patient data I will work with is anonymous and de-identified

iii) **Data Analysis:** Describe the procedures you will use to analyze the data/results.

- As the student, my role will be to analyze the behavioral visits data, which will include the questionnaires, tVNS, NDT, and autonomic data.
- Using the pre-existing data, I will run the following statistical analyses:
    (a) To determine if there is a positive effect using active tVNS relative to sham tVNS during the NDT (patients with FD vs. healthy control (HC)):
        (i) Two-way ANOVA
    (b) To compare HC and FD of Heart Rate Variability (HRV) data, first 6 minutes versus last 6 minutes of NDT sham versus active:
        (i) Non-parametric t-test
    (c) To compare FD vs. HC of the 6 Questionnaires (described below) :
        (i) Rank Sum
        (ii) Kruskal Wallace
- To analyze the autonomic data (which includes ECG data), NDT, and VAS, analyses will be run in:
    (a) Excel
    (b) Matlab
    (c) R
    (d) Kubios

c) **BIBLIOGRAPHY:** List major references (e.g. science journal articles, books, internet sites) from your literature review. If you plan to use vertebrate animals, one of these references must be an animal care reference.

i) Kuo, Braden. Auricular Vagal Nerve Stimulation for Gastric and Brain Outcomes. 2019. Massachusetts General Hospital, Boston, Massachusetts.

ii) Zagon, A. “Does the vagus nerve mediate the sixth sense?” Trends in Neurosciences, vol. 24, no. 11, 2001, pp. 671–673. doi:10.1016/s0166-2236(00)01929-9

iii) Englot, Dario J., et al. “Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy.” Neurosurgery, vol. 79, no. 3, 2016, pp. 345–353., doi:10.1227/neu.0000000000001165.

iv) Busch, Volker, et al. “The Effect of Transcutaneous Vagus Nerve Stimulation on Pain Perception – An Experimental Study.” Brain Stimulation, vol. 6, no. 2, 2013, pp. 202–209., doi:10.1016/j.brs.2012.04.006.

v) Lu, K.-H., et al. “Vagus Nerve Stimulation Promotes Gastric Emptying by Increasing Pyloric Opening Measured with Magnetic Resonance Imaging.” Neurogastroenterology & Motility, vol. 30, no. 10, 2018, doi:10.1111/nmo.13380.

vi) Meregnani, J., et al. “Anti-Inflammatory Effect of Vagus Nerve Stimulation in a Rat Model of Inflammatory Bowel Disease.” Autonomic Neuroscience, vol. 160, no. 1-2, 2011, pp. 82–89., doi:10.1016/j.autneu.2010.10.007.

vii) Hein, Ernst, et al. “Auricular Transcutaneous Electrical Nerve Stimulation in Depressed Patients: A Randomized Controlled Pilot Study.” Journal of Neural Transmission, vol. 120, no. 5, 2012, pp. 821–827., doi:10.1007/s00702-012-0908-6.

viii) Buijs, R. M., “The autonomic nervous system.” Handbook of Clinical Neurology, 1–11, 2013, doi:10.1016/b978-0-444-53491-0.00001-8

ix) Ylikoski, Jukka, et al. “Non-Invasive Vagus Nerve Stimulation Reduces Sympathetic Preponderance in Patients with Tinnitus.” Acta Oto-Laryngologica, vol. 137, no. 4, 2017, pp. 426–431., doi:10.1080/00016489.2016.1269197.

x) Clancy, Jennifer A. et al. “Non-invasive Vagus Nerve Stimulation in Healthy Humans Reduces Sympathetic Nerve Activity.” Brain Stimulation, vol. 7, no. 6, pp. 2014, 871–877. doi:10.1016/j.brs.2014.07.031

xi) Paleczny, Bartlomiej, et al. “Inspiratory- and expiratory-gated transcutaneous vagus nerve stimulation have different effects on heart rate in healthy subjects: preliminary results.” Clinical Autonomic Research, 2019., doi:10.1007/s10286-019-00604-0

xii) Mercante, Beniamina et al. “Auricular Neuromodulation: The Emerging Concept beyond the Stimulation of Vagus and Trigeminal Nerves.” Medicines, 2018, vol. 1, 10.doi:10.3390/medicines5010010

xiii) Mogilevski, Tamara et al. “Review article: the role of the autonomic nervous system in the pathogenesis and therapy of IBD.” Alimentary Pharmacology & Therapeutics. 2019, doi:10.1111/apt.15433