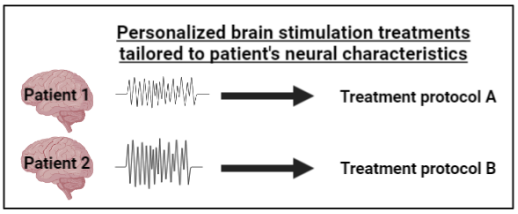
Elisa Kallioniemi, Ph.D.
Research Statement



Kallioniemi Lab's overview: The long-term vision of my research program is to *increase the efficacy of brain stimulation treatments by applying neural engineering approaches that allow personalizing brain stimulation to an individual's neural features*. Personalized protocols allow targeting the treatment to each individual's needs, thus treating both current treatment responders and non-responders. To reach this vision, my Lab will have three Research Thrusts: 1) study how individuals' neural features influence brain stimulation outcome, 2) determine how brain stimulation-induced electric field's features influence outcome, 3) develop more accurate brain stimulation methodology to evaluate neural features. This work is significant, as many people with brain disorders, psychiatric or neurological, cannot tolerate or do not benefit from available pharmaceuticals. Thus, targeted clinical research on non-pharmacological treatment options such as brain stimulation is vital for alternative, efficient treatments.

Why am I a unique researcher in the field and the best candidate to do this research? As an engineer, physicist, and neuroscientist with industrial and clinical experience in brain stimulation, I have a comprehensive perspective on brain stimulation and can combine advanced knowledge from these fields to develop innovative next-generation brain stimulation applications. I am also one of the few researchers developing brain stimulation methods to study the brain.

Introduction to the current state of brain stimulation: Electromagnetic brain stimulation applies external electricity, transported via magnetic fields through the scalp and skull to the brain. When the magnetic field reaches the brain's surface, it induces a small electric field that can generate action potentials in neurons. Depending on the applied stimulation protocol, repeated brain stimulation can strengthen or inhibit synaptic processes, enabling its use as a potential treatment in neurological and psychiatric disorders. Excitatory and inhibitory brain mechanisms govern the synaptic plasticity-related changes induced by brain stimulation. Unlike pharmaceuticals, brain stimulation is not associated with any frequent, long-lasting side effects if properly administered. In addition to treating (*Kallioniemi et al., 2019, in prep.1, 2*), a widely used brain stimulation technique, called transcranial magnetic stimulation (TMS), can also study brain function (*Kallioniemi et al., 2014, 2015a-e, 2016a,b, 2018, 2021*). TMS is a unique tool as when combined with a neurophysiological method, such as electroencephalography or electromyography, it can evaluate neural features unattainable with other methods. Especially, TMS can separate the excitatory and inhibitory brain mechanisms which govern the brain stimulation-induced effects (*Kallioniemi et al., 2014, 2018*). Thus, TMS is one of the best tools to study the mechanisms and effects of brain stimulation. When considering brain stimulation treatments, differences in excitatory and inhibitory brain mechanisms between individuals are critical because, in several disorders, these characteristics are distinct in treatment responders and non-responders (*Kallioniemi et al., in prep.1*). However, all treatments are currently applied as "one-size-fits-all" protocols, and only about 30% of patients benefit from the treatments. To treat the rest, 70%, we would need different protocols, i.e., personalize the treatment to their neural features.

Current gaps in brain stimulation preventing personalizing treatments

There are currently two major gaps in our knowledge preventing us from personalizing brain stimulation treatments:

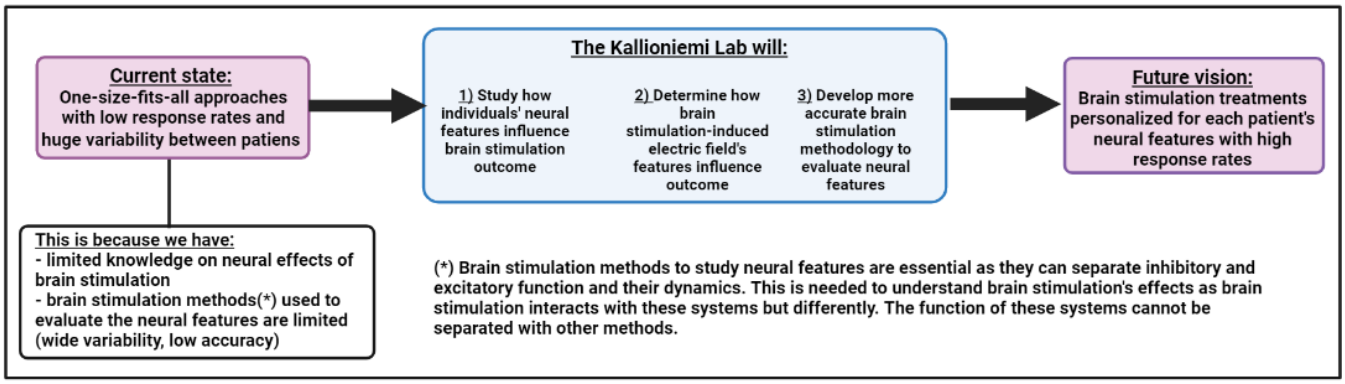
- We have very little understanding of how to match electromagnetic brain stimulation protocols with each brain disorder/patient as we do not understand the interactions between brain stimulation and neural features (***tackled in Kallioniemi Lab's Research Thrusts 1 and 2***). My research has shown

that small changes in brain stimulation parameters could induce vastly different neural effects (*Kallioniemi et al., 2016b, 2018, 2021*).

- Brain stimulation methods to study brain function are crucial in understanding the interactions between brain stimulation and neural features. However, the challenge with these brain stimulation methods is that they produce highly variable results (***tackled in Kallioniemi Lab's Research Thrust 3***). My research has shown that we can improve the accuracy of these methods by adjusting the brain stimulation protocols (*Kallioniemi et al., 2014, 2016b, 2018, 2021*).

My previous and current research: During my Ph.D. training, I developed novel TMS methodology to study cortical functions and obtained expertise in optimizing TMS parameters to induce more substantial neural effects. For example, I created a TMS method evaluating the state of the cortical inhibitory system independently of that of the excitatory system (*Kallioniemi et al., 2014*). Because the inhibitory and excitatory systems may be impaired differently, this method could provide a valuable biomarker for therapeutic applications. In addition, I advanced the TMS motor mapping methodology with several improvements making the procedure more accurate and providing information not received with conventional methods (*Kallioniemi et al., 2015d, 2016a,b*). These could improve clinical outcomes, e.g., in presurgical motor mapping before tumor resection or epilepsy surgery. I also showed that although TMS is a functional tool, it can evaluate cortical structure as TMS-induced electric fields only activate neurons from certain angles and developed a method for this (*Kallioniemi et al., 2015a,e*). During my postdoc, I have received training in brain stimulation applications targeted to treating psychiatric disorders. For instance, I have shown that the state of cortical inhibitory and cholinergic systems could determine whether an individual with severe depression benefits from repetitive TMS (rTMS) treatments (*Kallioniemi et al., in prep.1*). I also showed that rTMS treatments in Schizophrenia could restore part of the abnormal thalamocortical activity associated with the disorder (*Kallioniemi et al., in prep.2*). I have also been active in method development, and currently I collaborate with international researchers to develop guidelines for the combined TMS-EEG methodology (*Hernandes-Pavon et al., in prep.*).

Work conducted in the Kallioniemi Lab: My Lab's research will combine my expertise in brain stimulation methodology development, experimental skills, and clinical experience. My research will advance brain stimulation in all brain disorders.



Here are the overviews of the three Research Thrusts in the Kallioniemi Lab:

1. Study how individuals' neural features influence brain stimulation outcome

A) Summary: This research thrust will focus on understanding how outcomes will change when keeping brain stimulation constant but varying the neural features of the study population.

B) Background and the knowledge gap: There are indications that neural features impact how an individual reacts to brain stimulation (*Kallioniemi et al., in prep.1, Kallioniemi K99/R00 pilot data*), but we do not understand how. For example, aging changes the neural features (*Kallioniemi et al., submitted*), and brain disorders have different neural activity levels (*Kallioniemi K99/R00 pilot data*).
C) Short-term goal (~5 years): Determine how the individual's neural activity level (high vs. low) influences the neural and clinical effects of brain stimulation.
D) Long-term goal (~10-15 years): Determine how the age and sex of the individual influence the neural and clinical effects of brain stimulation.
E) Approaches: Apply different neuroimaging-guided brain stimulation protocols (rTMS), i.e., those that induce neural inhibitory effects and those that induce excitatory effects and evaluate, e.g., the magnitude and duration of induced changes.

2. <u>Determine how brain stimulation-induced electric field's features influence outcome</u>
A) Summary: This research thrust focuses on understanding how changing the electric field's features, such as strength, dosage, and pulse frequency, influence outcomes.
B) Background and the knowledge gap: Small changes in electric field features may substantially affect outcomes (*Kallioniemi et al., 2016b, 2018, 2021*), but we do not understand how to change electric field properties to receive a specific outcome.
C) Short-term goal (~5 years): Determine the relationship between different electric field pulse frequencies and neural and clinical effects.
D) Long-term goal (~10-15 years): Determine the relationship between electric field dosage and neural and clinical effects.
E) Approaches: Apply different neuroimaging-guided brain stimulation protocols (rTMS), i.e., those that induce neural inhibitory effects and those that induce excitatory effects, change their characteristics, and evaluate, e.g., the magnitude and duration of induced changes.

3. <u>Develop more accurate brain stimulation methodology to evaluate neural features</u>
A) Summary: This research thrust focuses on increasing the accuracy of brain stimulation methods evaluating neural features relevant for brain stimulation. Furthermore, a battery of techniques that could assess the features online and thus, provide instant feedback on the efficacy of brain stimulation will be developed.
B) Background and the knowledge gap: Brain stimulation methods evaluating brain function are vital as they can separate inhibitory and excitatory systems and their dynamics that cannot be done with any other methods. The challenge is that these methods include wide variability and poor reliability. My research has shown that the methods can be improved by adjusting the electric field properties.
C) Short-term goal (~5 years): Determine how electric field parameters influence the accuracy of protocols evaluating the cortical excitability and inhibitory systems' characteristics.
D) Long-term goal (~10-15 years): Develop a quick and reliable measurement battery to evaluate neural features online.
E) Approaches: Combine brain stimulation (TMS) with neurophysiological methods and evaluate the impact of changing electric field properties on methods evaluating neural features.

The Kallioniemi Lab will provide training possibilities in: neural engineering, brain stimulation, electromagnetic fields, neuroscience, neurophysiology, neuroimaging, biosignal processing, biostatistics, and clinical trials.

Potential funding targets: NSF CAREER, NIH R21, R01, R25, International Neuromodulation Society Innovative Research Grant Program, McKnight Technological Innovation in Neuroscience Award, Johnson & Johnson Scholars Award Program, and Brain & Behavior Research Foundation.

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