Concept Paper

Mechanistic Insights into Cerebrovascular Effects via Modal Analysis in Type 2 Diabetes and Dementia

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Mechanistic Insights into Cerebrovascular Effects via Modal Analysis in Type 2 Diabetes and Dementia

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Summary: Dementia, characterized by cognitive decline beyond age-related expectations, poses a formidable global health challenge. With an estimated 55 million individuals affected worldwide and 10 million new cases annually, dementia profoundly impacts memory, comprehension, language, and behavior. Then, the global diabetes population increased from 108 million in 1980 to 422 million in 2014, with a more rapid rise in prevalence observed in low- and middle-income countries compared to high-income countries. Individuals with diabetes have an increased risk of cognitive problems, including a higher likelihood of developing dementia, Alzheimer's disease, and vascular dementia, especially in older age. Managing diabetes through diet, physical activity, medication, and consistent screening and treatment for complications can prevent or delay its consequences. Globally ranking as the seventh leading cause of death, dementia's societal implications are substantial. The chapter delves into Mild Cognitive Impairment (MCI), a precursor to dementia, emphasizing its global epidemiological trends. Neuroimaging, particularly Functional Near-Infrared Spectroscopy (fNIRS), emerges as a non-invasive diagnostic tool, surpassing traditional imaging methods' portability. The chapter investigates the effects of transcranial electrical stimulation (tES) on neurovascular tissues, shedding light on its impact including potential to address metaboreflex related reduced exercise tolerance. Furthermore, the chapter presents a clinical trial examining the effects of a 2-month exercise program on cognitive function and muscular oxidative capacity in older adults with type 2 diabetes. The study's design, individualized exercise regimens to address muscle mechanoreflex and metaboreflex responses, and their physiological changes during exercise are discussed, offering insights into the interplay between exercise tolerance, cognition, and vascular health. The findings contribute to tailored and effective interventions for cognitive well-being. Here, our exploration extends to the application of tES in optimizing exercise performance, with a focus on its various forms, including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). A physiological modeling approach based on the neurovascular unit (NVU) is employed, revealing potential avenues for also treating vascular dementia (often noted to have a stronger association with type 2 diabetes) through tACS, guided by human-in-the-loop approaches. Here, modal analysis for control is applied to assess the NVU model's characteristic dynamics under tACS, providing a comprehensive understanding of neurovascular coupling modes. In summary, this chapter synthesizes diverse facets in type 2 diabetes comorbidity and cognitive decline, ranging from global impact and diagnostic criteria to innovative interventions like exercise and transcranial electrical stimulation. The multidisciplinary approach integrates epidemiology, clinical trials, and physiological modeling, contributing valuable insights into the holistic management of cognitive health and neurovascular function.

Keywords: cerebrovascular; neurovascular unit; physiological model; metaboreflex; tES

Background

Global Impact of Dementia: Dementia, a condition characterized by the deterioration of cognitive functioning beyond the expected age-related decline, poses a significant global health challenge. The World Health Organization estimates that 55 million individuals worldwide are currently living with dementia, with an additional 10 million new cases diagnosed annually [https://www.who.int/news-

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room/fact-sheets/detail/dementia#:~:text=Key%20facts,%2Dand%20middle%2Dincome%20countries]. This condition not only affects memory but also impacts comprehension, calculation, language, and judgment. Psychiatric manifestations, including changes in mood and behaviour, often accompany cognitive decline. Globally, dementia ranks as the seventh leading cause of death and contributes significantly to disability among the elderly. The ramifications of dementia extend beyond individual suffering, encompassing broader societal and public health implications (Nichols et al., 2022).

Types of Dementia: The Royal College of Psychiatrists identifies several subtypes of dementia, including Alzheimer's disease, vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, and frontotemporal dementia [https://www.rcpsych.ac.uk/improving-care/nccmh/service-design-and-development/dementia]. Alzheimer's disease, responsible for 60% of all dementia cases, is marked by a gradual onset of memory impairments associated with tau deposits affecting neurotransmission. Vascular dementia, linked to disrupted blood supply in the brain, presents memory loss, language difficulties, and physical problems. Dementia with Lewy bodies results from Lewy body deposits, leading to memory problems, confusion, and visual hallucinations. Frontotemporal dementia, arising from insults to the frontal areas of the brain, manifests with marked personality changes, behavioural alterations, and language difficulties.

Introduction to Mild Cognitive Impairment: Mild Cognitive Impairment (MCI) represents a less severe cognitive decline than dementia. Individuals with MCI remain functional, and experience milder memory impairment compared to dementia. Peterson et al.'s (Petersen et al., 1999) diagnostic criteria for MCI include memory complaints, normal daily activities, normal general cognitive functioning, abnormal memory based on age, and the absence of clinical signs of dementia. A global perspective on MCI and dementia reveals alarming trends. Li et al. (GBD 2016 Dementia Collaborators, 2019, 1990–2019) reported a significant increase in the incidence and prevalence of Alzheimer's disease and other forms of dementia. The Lancet study (Nichols et al., 2022) forecasting dementia prevalence by 2050 predicts a rise from 57.4 million cases in 2019 to 152.8 million cases. Efforts to address MCI and dementia are imperative given the high progression rates from MCI to Alzheimer's disease. Diabetes, prediabetes, and Metabolic Syndrome (MetS) were all linked to elevated risks of MCI progressing to dementia (Pal et al., 2018).

Advancement to dementia in individuals affected by diabetes, prediabetes, and metabolic syndrome: The global prevalence of diabetes increased significantly from 108 million in 1980 to 422 million in 2014, with a higher rise in low- and middle-income countries [https://www.who.int/news-room/fact-sheets/detail/diabetes]. Diabetes is a leading cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation, contributing to an estimated 2 million deaths in 2019. Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age. People with Type 1 diabetes face a higher risk of dementia, with a 93% increased likelihood according to a study. Older adults with type 1 diabetes, hospitalized for blood sugar extremes, are at elevated dementia risk, especially when experiencing both highs and lows. High blood sugar levels, common in type 2 diabetes, are strongly correlated with Alzheimer's disease, leading to increased beta-amyloid protein, a key Alzheimer's marker. Early-stage type 2 diabetes is associated with brain dysfunction, insulin resistance, and impaired glucose use for normal brain function. Individuals with Type 2 diabetes show accelerated cognitive decline, particularly in executive function and processing speed, with earlier onset increasing dementia risk. The impact of diabetes on the brain is linked to the blood protein hemoglobin A1C (HbA1C), affecting memory function and hippocampal size. The gene for amyloid precursor protein (APP), involved in Alzheimer's, also affects the insulin pathway disrupted in diabetes, suggesting a potential therapeutic target for both diseases. Prevention measures include adopting a healthy lifestyle with a balanced diet, regular exercise, maintaining normal body weight, and avoiding tobacco use, while the management of diabetes involves a combination of diet, physical activity, medication, and regular screening.

Assessment Guidelines: The National Institute for Clinical Excellence (NICE) (Overview | Dementia: assessment, management and support for people living with dementia and their carers | Guidance | NICE, 2018) provides guidelines for assessing cognitive impairment. History-taking,

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physical examination, blood and urine tests, and cognitive testing with validated tools are recommended for non-specialists. Specialists are advised to consider subtype-specific diagnosis, neuropsychological testing, and imaging to differentiate dementia subtypes.

Neuroimaging for Diagnosis and Screening: Neuroimaging plays a crucial role in differentiating dementia subtypes. Various tools, including fluorodeoxyglucose-positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI), aid in identifying specific patterns associated with Alzheimer's disease, frontotemporal dementia, and vascular dementia. Functional Near-Infrared Spectroscopy (fNIRS) emerges as a non-invasive and cost-effective alternative to traditional imaging methods (Pinti et al., 2020). While sharing similarities with functional MRI (fMRI) in measuring hemodynamic responses, fNIRS surpasses fMRI in portability, allowing assessments in naturalistic environments. Its application extends to psychiatry research, providing valuable insights into various psychiatric disorders, including schizophrenia, depression, bipolar disorder, and ADHD. fNIRS has proven instrumental in detecting characteristic changes in cerebral cortex hemodynamics associated with psychiatric disorders. Studies have shown alterations in frontal activation for schizophrenia, changes in oxyhemoglobin concentration for ADHD, and distinctive patterns for panic disorder, obsessive-compulsive disorder, and depression.

Normal brain function relies on regulated cerebral blood flow (CBF), a process compromised in vascular dementia, particularly subcortical ischemic dementia affecting cognitive abilities in the elderly (Zhao et al., 2023),(Zhao et al., 2022),(Li et al., 2021). This condition can result from cerebral microangiopathy e.g. in diabetes, leading to increased vessel stiffness and a presumed reduction in slow spontaneous oscillations (Lee et al., 2000),(Zhao et al., 2022),(Li et al., 2013). While the longitudinal recovery of CBF regulation in these cases remains understudied, cerebrovascular reactivity (CVR) – the change in CBF in response to vasoactive stimuli – could provide insights into the pathogenesis of CBF dysfunction. Existing literature uses stimuli like acetazolamide and carbon dioxide, but these have systemic effects (Fierstra et al., 2013). Transcranial electrical stimulation (tES) offers a promising approach to evoke CBF (Zheng et al., 2011) which may be partly effected by the arousal response (Arora and Dutta, 2022). However, the role of autonomic function in regulating CBF is not fully understood, and the contribution of the baroreflex in CBF regulation is debated (Ogoh and Tarumi, 2019). While acute increases in systemic blood pressure trigger peripheral vasodilation via baroreflex, cerebral vasculature may need to constrict to protect the blood-brain barrier. Unlike the expected response, acute hypertension does not decrease CBF or cause cerebral vasodilation. Regional differences in autonomic outflow between systemic and cerebral blood vessels are possible. Additionally, the impact of direct (autonomic regulation) and indirect (systemic blood pressure regulation) baroreflex influences on CBF may vary. In hypertensive patients, sympathetic nerve activation leads to cerebral vasoconstriction, unlike in normotensive individuals. The complex interplay of arterial baroreflex with other factors like cardiac output, respiratory chemoreflex, and physiological conditions such as cardiovascular disease, complicates understanding CBF regulation. Despite challenges in identifying its role, the arterial baroreflex's significance in maintaining adequate CBF, especially in disease conditions, should be acknowledged and investigated as a biomarker.

Effect of the sympathetic nervous system on cerebral oxygenation in patients with type 2 diabetes [by Seyyed Alireza Hosseini Kakhak]: Diabetes mellitus (T2DM) is the fourth cause of death among non-communicable diseases and accounts for 2 million deaths annually worldwide. The prevalence of diabetes is increasing dramatically, especially in low- and middle-income countries than in high-income countries. (https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases).

T2DM is associated with serious microvascular or macrovascular complications in many organs and systems that lead to a cluster of diseases including heart disease and stroke, peripheral arterial disease, retinopathy, nephropathy, peripheral neuropathy, and lower-extremity amputations (Deshpande et al., 2008). Cardiovascular disease (CVD), where the coronary and blood vessels are negatively affected, is the main cause of death in patients with T2DM (https://diabetes.org/about-diabetes/complications/cardiovascular-disease)

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A lesser-known aspect of cardiovascular disorders associated with T2DM is the condition in which T2DM leads to increased sympathetic nervous system (SNS) activity – see Figure 1. Therefore, although exercise is known as a valid, effective, non-expensive, and side-effect-free modality in the management and treatment of T2DM, patients feel more effort, difficulty, and trouble during exercise, and this may lead to the unwillingness of these patients to exercise and show poor adherence to exercise (Doneddu et al., 2020).

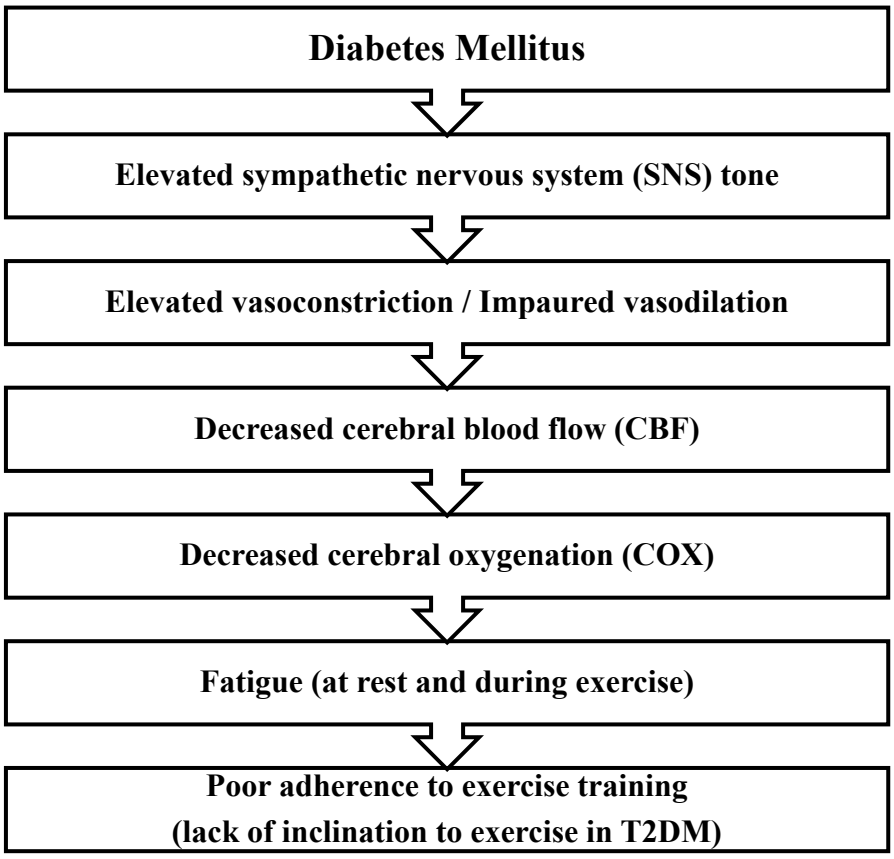

Figure 1. Schematic illustration of the effect of the sympathetic nervous system (SNS) on cerebral oxygenation (COX) in patients with type 2 diabetes (T2DM) (By Hosseini-Kakhak and Anirban 2023).

In support of this claim, our studies show that during exercise, SNS tone dramatically increased in patients with T2DM, which results in elevated vasoconstriction, which means these patients have limited vasodilatory capacity (Roberto et al., 2019). During exercise, cerebral blood flow (CBF) and hence cerebral oxygenation (COX) increases in normal and healthy people. Any condition that impairs CBF may lead to fatigue. It has been shown that during exercise training, CBF is impaired in T2DM which may be because of SNS hyperactivity. This event leads to a decrease in COX and therefore induction of fatigue. In line with this evidence, we found that in patients with T2DM, concurrent performing a mental task (MT) and metaboreflex could not enhance COX in the same amount of healthy people. So, COX can be a limiting factor in physical performance in T2DM patients (Doneddu et al., 2020).

Brain and muscle oxygenation changes after 2-month exercise in sedentary older adults with diabetes [by Fei Zhao]: Abnormalities in the muscle metaboreflex contribute to reduced exercise tolerance and increased cardiovascular risk (Gama et al., 2021),(Nesti et al., 2020). Although exercise training is known to benefit neurocardiovascular function, its impact on the muscle metaboreflex is still debated. Some studies suggest that exercise training enhances the sensitization of muscle metabolically afferents and improves neurocardiovascular responses to muscle metaboreflex activation, while others report no significant changes. Possible mechanisms for improvement include heightened sensitivity of channels and receptors, increased antioxidant capacity, reduced metabolite

accumulation, improved functional sympatholysis, and enhanced muscle perfusion. Therefore, there is a need to explore the dose-response relationship of different exercise components and modalities in individuals with both intact and impaired muscle metaboreflex, as well as investigate specific mechanisms underlying metaboreflex improvements in T2DM (Nesti et al., 2020). Our 2-month moderate-intensity exercise intervention clinical trial was pre-registered on ClinicalTrials.gov (NCT04626453 and NCT04812288). It included two groups: an Intervention group comprising older sedentary adults with type 2 diabetes (T2DM) and a control group consisting of healthy older adults, encompassing both active and sedentary individuals.

Multidomain Interventions for Cognitive Enhancement: Ngandu et al. (Ngandu et al., 2015) trial emphasized the importance of addressing modifiable risk factors for dementia and the multidomain intervention involving diet, exercise, cognitive training, and vascular risk monitoring on cognitive performance in older individuals at risk from the general population to enhance or preserve cognitive performance and its implications for older individuals at risk. However, irregularities in the muscle metaboreflex contribute to reduced exercise tolerance in T2DM (Doneddu et al., 2020),(Kim et al., 2015).

Exercise Intervention for Type 2 Diabetes-Related Cognitive Impairment: We conducted a clinical trial (NCT04626453 and NCT04812288) targeting cognitive impairment in individuals with type 2 diabetes through a tailored aerobic and resistance exercise regimen aligned with the recommendations of the American College of Sports Medicine (Zhao et al., 2019). We highlighted the design of a 2-month individualized progressive moderate-intensity exercise intervention, including prospective registration at ClinicalTrials.gov and the involvement of two groups: an Intervention group comprising older sedentary adults with type 2 diabetes and a Control group consisting of healthy older adults. This study aimed to investigate the impact of a 2-month moderate-intensity aerobic-and-resistance exercise on various health parameters in sedentary older adults with T2DM. The participants underwent personalized progressive exercise, with assessments before and after the intervention. Results showed positive changes in glucose attached hemoglobin (HbA1C), cognitive and physical performance, as well as brain and muscle oxygenation. The exercise program contributed to improved basic executive function, lower extremity function, and endurance in the diabetes group. Brain overactivation reduced, and differences between the diabetes group and control groups decreased by 40% in cognitive and physical tests. The study suggests that this exercise regimen could be beneficial for individuals with compromised oxidative capacity, such as those with cardiovascular diseases or other cognitive illnesses. The exercise effects on the muscles were monitored using the following optical neuroimaging measures (Zhao et al., 2019) – see Figure 2.

Resting SmO2 (Tissue Oxygen Saturation at Rest): Resting SmO2 refers to the baseline level of tissue oxygen saturation in a muscle or specific tissue region while an individual is at rest. SmO2 is a measure of the percentage of oxygenated hemoglobin in the total hemoglobin present in the tissue. Resting SmO2 provides a baseline measurement before any physical activity or exercise, offering insight into the oxygenation status of the tissue under normal, non-stressful conditions.

SmO2 Drop During Exercise: SmO2 drop during exercise refers to the gradual decline or "drop" in tissue oxygen saturation observed during sustained physical activity. As an individual engages in exercise, there is an increased demand for oxygen by working muscles. SmO2 drop reflects the gradual decrease in tissue oxygen saturation as oxygen is utilized by muscles for energy production. Monitoring SmO2 drop during exercise helps assess how well oxygen delivery matches the oxygen consumption requirements during the activity.

SmO2 Recovery After Exercise: SmO2 recovery after exercise refers to the rate at which tissue oxygen saturation returns to its baseline level following the cessation of physical activity. After exercise, the body continues to consume oxygen to restore energy reserves and clear accumulated metabolic byproducts. SmO2 recovery is a measure of how efficiently the tissue regains its baseline oxygen saturation level, reflecting the ability of the cardiovascular and respiratory systems to meet the post-exercise oxygen demands and support recovery. Faster recovery may indicate better oxygen utilization efficiency (Wang et al., 2006).

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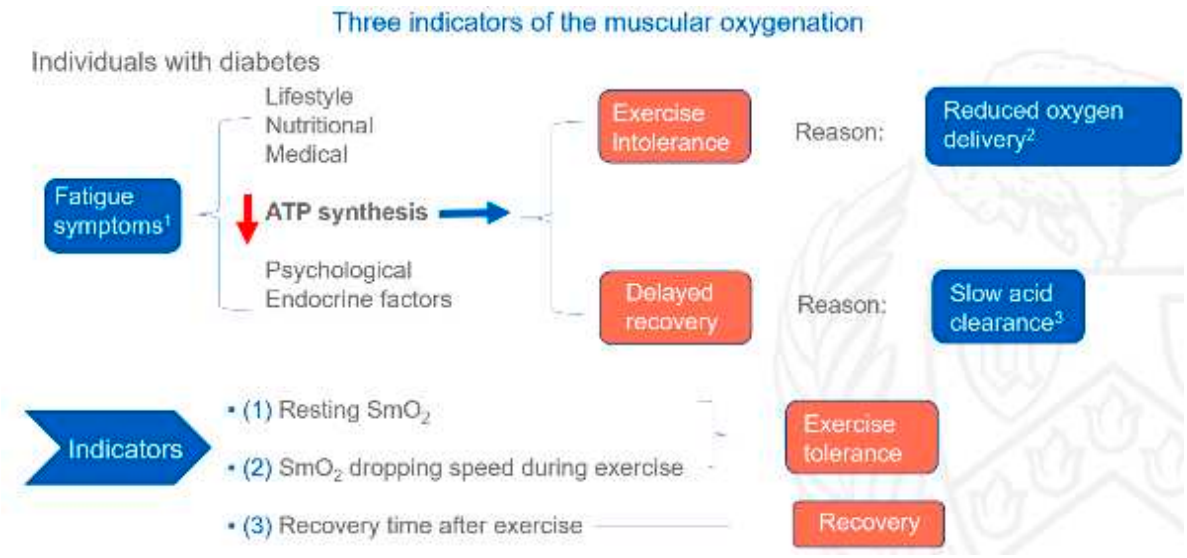

Figure 2. Postulated indicators of the muscle oxygenation response – resting SmO2, SmO2 drip during exercise, SmO2 recovery after exercise.

Practicality and Feasibility of Individualized Home-Based Exercise Programs: We found (Zhao et al., 2023) a remarkable completion rate (89.14%) observed during the 2-month moderate intensity individualized and progressive exercise program, highlighting its practicality, feasibility, and excellent tolerance, particularly during the COVID-19 pandemic. This is postulated to be successful due to individualization which addressed the metaboreflex limitations (Doneddu et al., 2020) highlighted in the previous section. Participants in the study followed a combined exercise regimen, adhering to guidelines from the American College of Sports Medicine (ACSM). To determine the baseline exercise intensity, we let participants choose a comfortable ankle weight for knee flexion and extension and tested the maximum number for both movements. The program included progressive resistance exercises and brisk walking six days a week. Participants chose one rest day each week and were encouraged to engage in 20-minute sessions of both resistance and aerobic exercises. The resistance exercises focused on major muscle groups, reduced to four movements, and included ankle weights for knee extension and flexion, chair-stand, and heel raises. For the resistance exercises, participants performed 3-4 sets with a 30-second break between sets. The intensity and progression were personalized, and the number of repetitions increased gradually. Walking sessions, considered moderate-intensity exercise, were determined based on heart rate reserve (HRR) calculations and participants' maximum walking speed from the 6 Minute Walking Test. The walking duration ranged from 8-15 minutes per session.

The study incorporated safety measures, including individualized resting times and indoor walking to prevent tripping hazards. Participants received biweekly phone calls to monitor safety, satisfaction, and adherence. The adherence rate for the 2-month exercise program was high, with participants achieving a mean score of 89.14%. The exercise program aimed to enhance or preserve cognitive performance and physical well-being in older adults with T2DM.

Physiological Changes and Brain Response: Examining the Zhao et al. (Zhao et al., 2019) study, we found significant decreases in muscle oxygen saturation during specific tasks and post-intervention changes in prefrontal activation (Zhao et al., 2022). Our study observed improvements in muscle oxygenation during physical tests. The design of the exercise regimen, tailored to individual capacities, contributed to the effectiveness of the program. Similar studies in other populations support the positive effects of exercise on mitochondrial function and glucose tolerance. The findings align with studies that measured muscle oxygenation during physical tests, indicating an improvement in muscle oxidative metabolism. However, the study did not find a significant improvement in muscle oxygenation recovery after physical tasks, suggesting the need for a longer exercise period to achieve further enhancements.

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We also analyzed task-related hemodynamic brain responses suggesting higher cognitive effort and a surge in cerebral blood flow. Figure 3 shows the results from our study (Zhao et al., 2023) where the difference between the hemodynamic response functions (HRFs) of the healthy controls and T2DM intervention group illustrates the mental stress (due to cognitive task) related early "surge" in cerebral blood flow in T2DM with solid line showing oxyhemoglobin concentration changes (Figure 3d,e). In contrast, the healthy controls have an "initial dip" in the cognitive task related oxyhemoglobin concentration changes (Figure 3c,d). Here, it is postulated that elevated levels of circulating epinephrine in T2DM (Yufu et al., 2014) enhance the blood pressure responses to mental stress and systemic blood pressure regulation through the arterial baroreflex influences cerebral blood flow and cerebral function (Ogoh and Tarumi, 2019). Then, our exercise regimen resulted in a reduced "surge" in oxyhemoglobin concentration changes (Figures 3e versus 3d) during medium-difficulty cognitive tasks, indicating a positive effect on cognitive function and possibly better systemic blood pressure regulation through the arterial baroreflex. While similar studies have been conducted in frail older adults and those with mild cognitive impairment (Ogoh and Tarumi, 2019), our research focused specifically on older adults with T2DM.

Our study observed statistically lower brain activation during clock drawing at follow-up but not during memory tasks and the Trail Making Test (TMT). The findings differed from a study on frail older adults without diabetes, suggesting that exercise-induced improvements may vary based on exercise duration and population characteristics. T2DM increases the risk of cognitive impairments, and the study emphasized the need to understand how exercise influences brain structure and function. The results provided evidence of pathological changes in the brain among older adults with T2DM reflected in the low frequency hemodynamic oscillations (Zhao et al., 2022).

Regarding cognitive performance, the study found mixed results on memory improvement, suggesting that the duration of exercise may play a role. Executive function, assessed by the Trail Making Test, showed improvement in the study participants. However, differences in cognitive tests and participant age may explain discrepancies with other studies. The study also compared brain activation between T2DM and healthy older adults during cognitive tasks. Brain overactivation was observed in older adults with T2DM and the choice of cognitive tests influenced the brain regions exhibiting overactivation (Zhao et al., 2022). The study highlighted the potential compensatory role of brain overactivation and the positive impact of exercise on mitigating these effects. Understanding brain mechanisms during cognitive tasks enhances the knowledge of exercise interventions for cognitive health.

In summary, the study demonstrated the beneficial effects of a 2-month individualized progressive exercise program on cognitive function and muscular oxidative capacity in older adults with T2DM. The findings contribute to the understanding of moderate intensity exercise interventions for cognitive health and highlight the importance of individualized exercise regimens to address the metaboreflex related reduced exercise tolerance in T2DM (Kim et al., 2015),(Nesti et al., 2020). We also highlight the potential for monitoring intervention effects and personalizing exercise regimens based on individual brain responses, paving the way for more targeted and effective exercise interventions.

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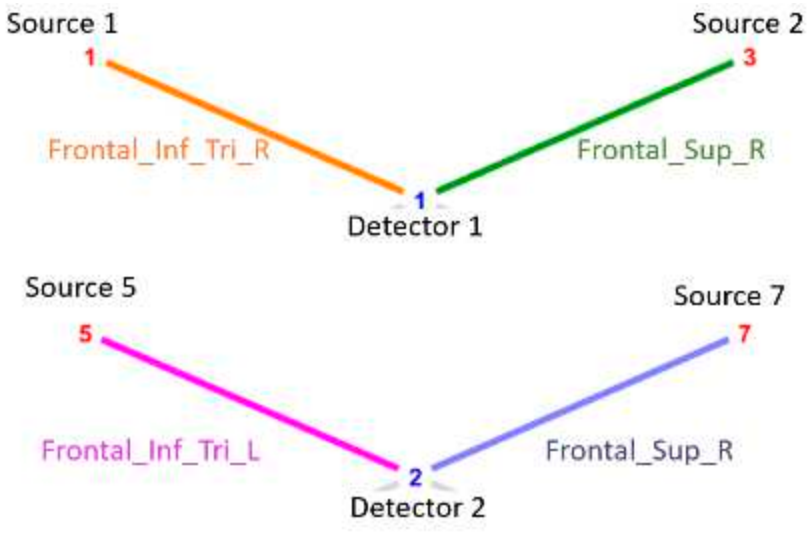

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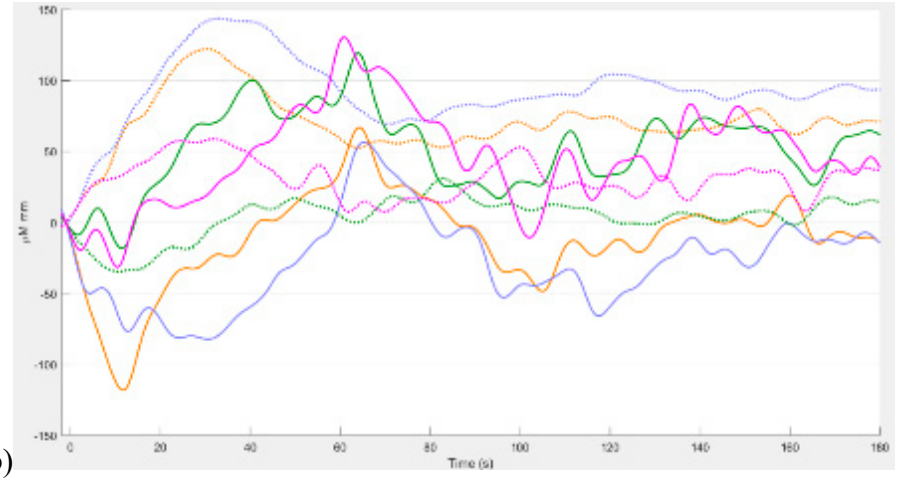

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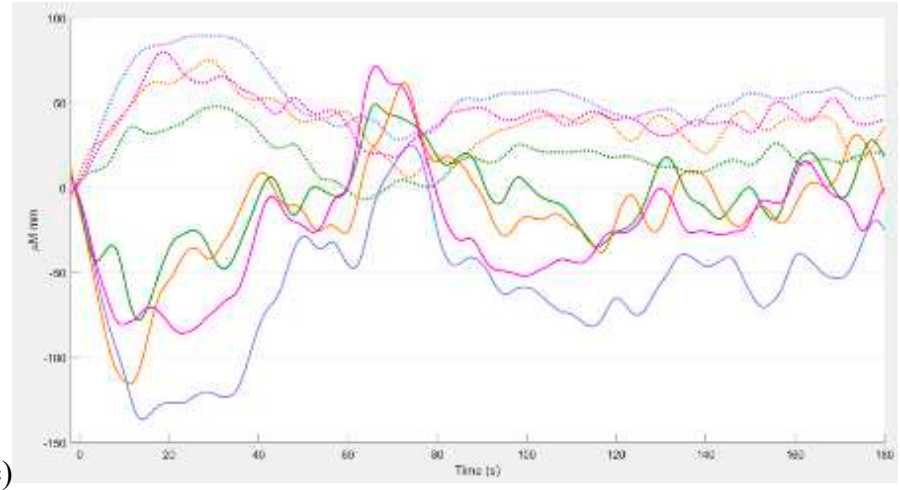

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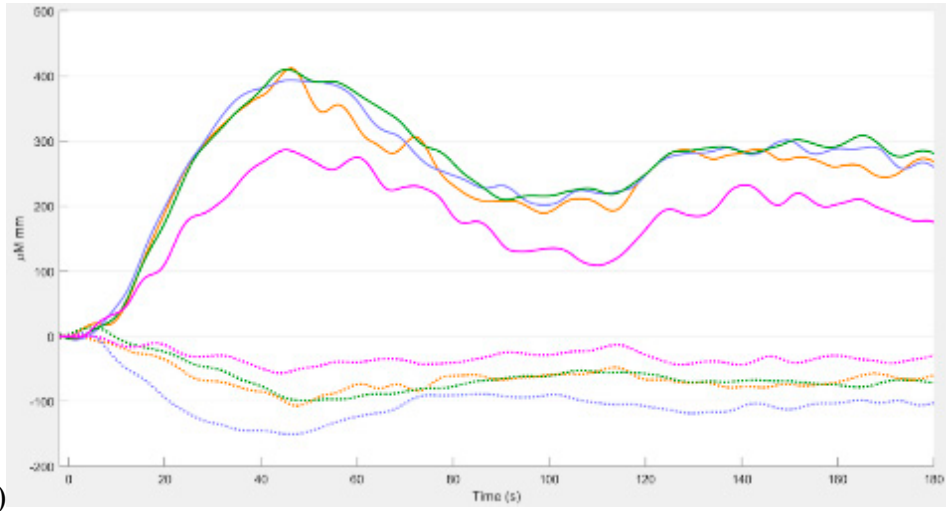

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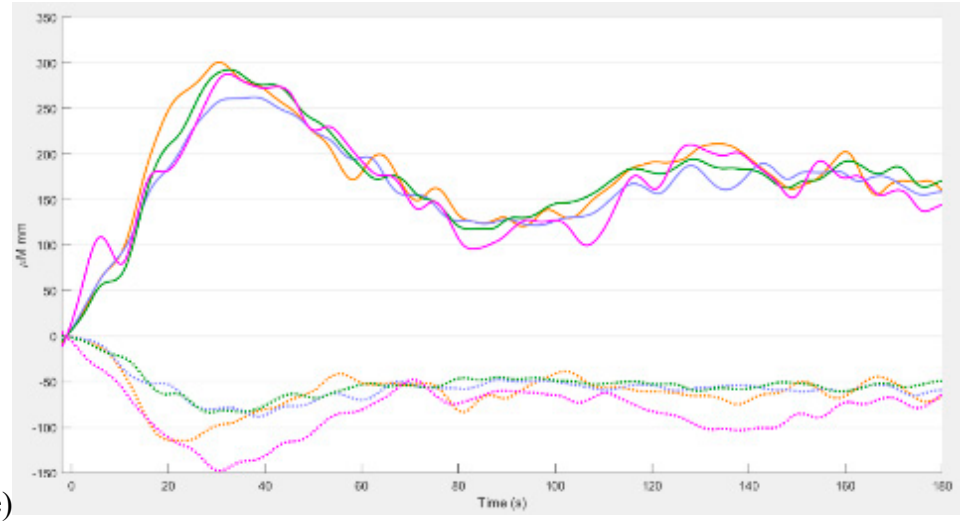

Figure 3. Averaged hemodynamic response function (HRF) of the experimental groups with solid line showing oxyhemoglobin concentration changes and the dotted line showing the deoxyhemoglobin concentration changes. (a) Optode montage with colors denoting different prefrontal brain regions of interest. (b) Sedentary healthy control group HRFs. (c) Active healthy control group HRFs. (d) T2DM intervention group pre-intervention HRFs. (e) T2DM intervention group post-intervention HRFs.

Non-invasive electrical stimulation for priming cerebral hemodynamics (by Yashika Arora and Marcel Stefanski)

In the systematic review by Machado and colleagues (Machado et al., 2019) and meta-analysis of 22 studies involving 393 participants, the effects of transcranial Direct Current Stimulation (tDCS) on exercise performance were examined. Weak evidence suggested a significant positive effect of anodal tDCS (a-tDCS) over the motor cortex (M1) on time to exhaustion (TTE) in cycling, but results were influenced by a single study. No significant effects were found for cathodal tDCS (c-tDCS) on TTE. For isometric muscle strength, no significant effects were observed for a-tDCS applied before or during exercise. Mixed results were reported for isokinetic muscle strength. A quantitative synthesis indicated a significant improvement in cycling performance with a-tDCS over M1, but caution is advised due to the influence of a single study. Commercial tDCS devices for exercise performance were not addressed in peer-reviewed studies, raising safety and efficacy concerns. Methodological aspects, including individual variability and optimal tDCS parameters, need further exploration in future research.

In our opinion, transcranial electrical stimulation (tES) can improve exercise performance when individually customized for priming hemodynamic response (Dutta, 2015),(Guhathakurta and Dutta,

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2016),(Arora et al., 2021),(Arora and Dutta, 2022) to address detrimental cerebral effects of metaboreflex (Roberto et al., 2019),(Doneddu et al., 2020) during exercise interventions. Then, neuromuscular electrical stimulation can also have beneficial cerebral hemodynamic effect (Dutta et al., 2021) during exercise interventions. Different forms of tES have varying current profiles. For tES, transcranial direct current stimulation (tDCS) uses a monophasic, non-oscillating baseline, while transcranial alternating current stimulation (tACS) involves rhythmically reversing the electron flow. Other methods include transcranial oscillating current stimulation (tOCS), using a direct component to guide oscillations, and transcranial random noise stimulation (tRNS), injecting alternating current with bounded stochasticity (Guleyupoglu et al., 2013),(Paulus, 2011). Neurovascular modulation occurs in various stimulation protocols, with mechanisms not fully understood. As tES affects blood vessels through neuronal or non-neuronal cells, a deeper understanding of signaling pathways is crucial. tACS, unique in manipulating intrinsic oscillations, may hold promise for treating vascular dementia (Antal and Paulus, 2013),(Helfrich et al., 2014) when applied with a human in the loop approach (Arora and Dutta, 2022) – see Figure 4.

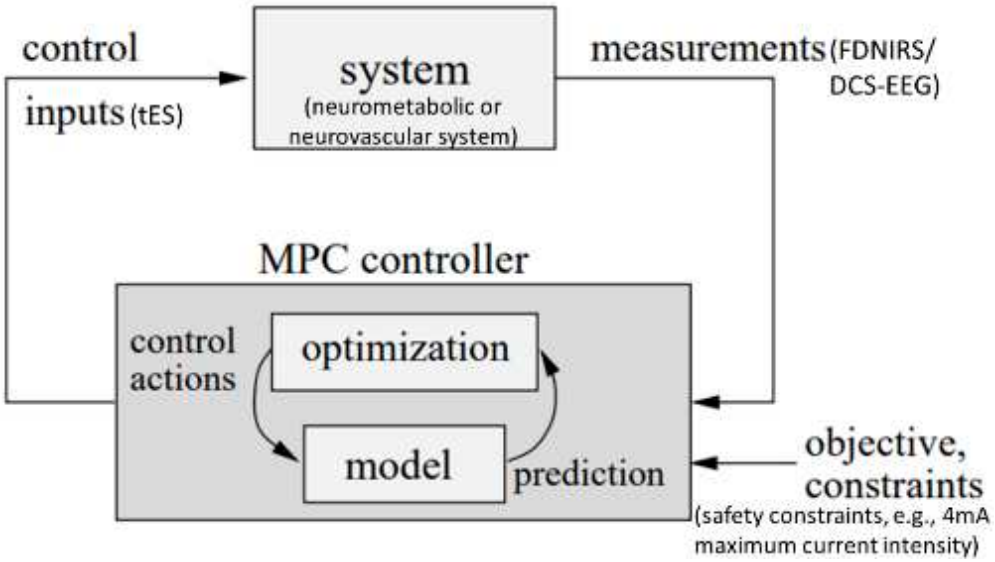

Figure 4. Illustration of model predictive control (from (Arora and Dutta, 2022)).

In this chapter, we present our physiological modelling approach (Arora et al., 2021),(Arora and Dutta, 2022) based on the physiology of neurovascular tissues for assessing the vascular response to electric fields generated by tES through various pathways in neurovascular unit (NVU). Our studies (Arora et al., 2021),(Arora and Dutta, 2022) presented a physiological model that incorporated the NVU components, including vascular smooth muscle, perivascular space, synaptic space, and astrocyte cell. The model aimed to capture the effects of transcranial electrical stimulation (tES), specifically transcranial alternating current stimulation (tACS), on direct and indirect vascular responses. Four nested NVU compartmental pathways were proposed, allowing the simulation of tES-induced vessel volume responses.

The tES current density, acting as an input pulse, perturbed state variables in each NVU compartment. The study considered four simulated pathways for vessel response modulation: synaptic potassium, astrocytic membrane potential, perivascular potassium currents, and voltage-gated ion channels on smooth muscle cells. These pathways were designed to simulate vessel oscillations within the frequency range <0.2 Hz, controlled by nonlinear calcium dynamics. Modal analysis (Rogers, 2000),(Modal Analysis - 1st Edition, n.d.), a technique commonly used in structural and fluid mechanics (Modal Analysis for Damage Detection in Structures | Semantic Scholar, n.d.), was applied to derive the characteristic dynamics of the NVU model. Modal analysis involves determining the system's natural frequencies, mode shapes, and damping factors, allowing the

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development of a mathematical model describing the system's behaviour. While modal analysis is traditionally used in engineering fields, the study applied this approach to analyse the NVU model, specifically focusing on evaluating neurovascular coupling modes induced by tACS. Then, the design of controls is imperative to modify the natural behaviour of interconnected synchronous generators in NVU systems. Despite the inherent nonlinearity of NVU systems, accurately predicting oscillations around an operating point is possible through linearized system models (Arora et al., 2021). This justifies the application of linear control theory for the design of oscillation controls (Rogers, 2000).

fNIRS of transcranial electrical stimulation effects on hemodynamics: The examination of transcranial electrical stimulation (tES) effects, both immediate and prolonged, is a critical area of interest in our neuroscientific research (Arora et al., 2021). We examined an fMRI-tES dataset (Arora and Dutta, 2023) with a TR of 3.36 seconds, revealing similar finite impulse response hemodynamic response function "FIR HRF" model (with RH, TTP, and FWHM using the rsHRF toolbox (Wu et al., 2021)) in anodal and sham tDCS conditions at the electrode locations FC5 and PZ ROIs, but differing in the electrode location FP2 ROI. This discrepancy may be linked to local cortical inhibitory circuits, perivascular nerves, and astrocyte stimulation (Arora and Dutta, 2023). Here, our prior computational analyses proposed direct perivascular nerve and astrocyte stimulation during tDCS onset (Arora et al., 2021),(Arora and Dutta, 2022). Our prior findings also indicate perivascular space changes (https://www.ismrm.org/workshops/2022/Neuromodulation/program.php), that may also raise safety concerns for higher intensity 4 mA stimulation especially in pathological tissues. Then, tES is postulated to also impact blood-brain barrier permeability, influencing neuronal function (Shin et al., 2020), that also raises safety concerns. Then, transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) differ in current profiles, with different therapeutic and safety implications. Indeed, short-duration tDCS can have physiological effects, impacting arousal and hemodynamics response (Arora and Dutta, 2022), which may have better therapeutic implications than longer duration. Here, we suggest short duration ON-OFF tDCS time series (see Figure 1 in (Dutta, 2015)) acting as slow transcranial oscillating-current stimulation (tOCS) (Arora and Dutta, 2022) may act through superficial nerves, noradrenergic axons, and efferent innervation to evoke beneficial hemodynamic response. Then, sympathoexcitation, reflected in pupil dilation (Arora and Dutta, 2022), may impact glucose regulation. Therefore, mechanistic understanding of glucose-neurovascular tissue interaction during tES is crucial (Arora and Dutta, 2022). Sympathoexcitation may affect smooth muscle cells, particularly in arterioles with specific oscillatory frequencies which may be suitable for frequency domain analysis (Arora and Dutta, 2022).

Understanding the modulatory effects of tES on blood vessels necessitates exploring multiple pathways within the neurovascular unit (NVU). Unravelling these signalling pathways is crucial for comprehending tES effects on neurons and blood vessels to developing therapeutics, as discussed by Arora et al. (Arora et al., 2021) – see Figure 5a. The stimulation evoked cerebral blood flow (CBF) changes depends on multiple pathways including sympathetic vascular tone (stimulus related norepinephrine released from sympathetic efferent nerves modulates vascular tone (Sheng and Zhu, 2018)) against which the neurovascular coupling need to act to dilate the blood vessels (Arora and Dutta, 2022). Indeed, neurovascular coupling itself may be modulated (Dutta, 2021a) since noradrenaline release from locus coeruleus axons induces vascular tone in arteriolar smooth muscle and contractile capillary pericytes (Korte et al., 2023). This tone enables neuronal activity to trigger vasodilation, enhancing local cerebral blood flow. In the brain, a significant portion of vascular resistance is in capillaries, and locus coeruleus axons release noradrenaline closer to pericytes than to arterioles. Therefore, in our opinion, modulation of the vascular tone needs to well-coordinated with the neurovascular coupling related effects for adequate CBF response to task and stimulation related metabolic needs (which may be compromised in diabetes (Zhao et al., 2023)) that may be facilitated with tES.

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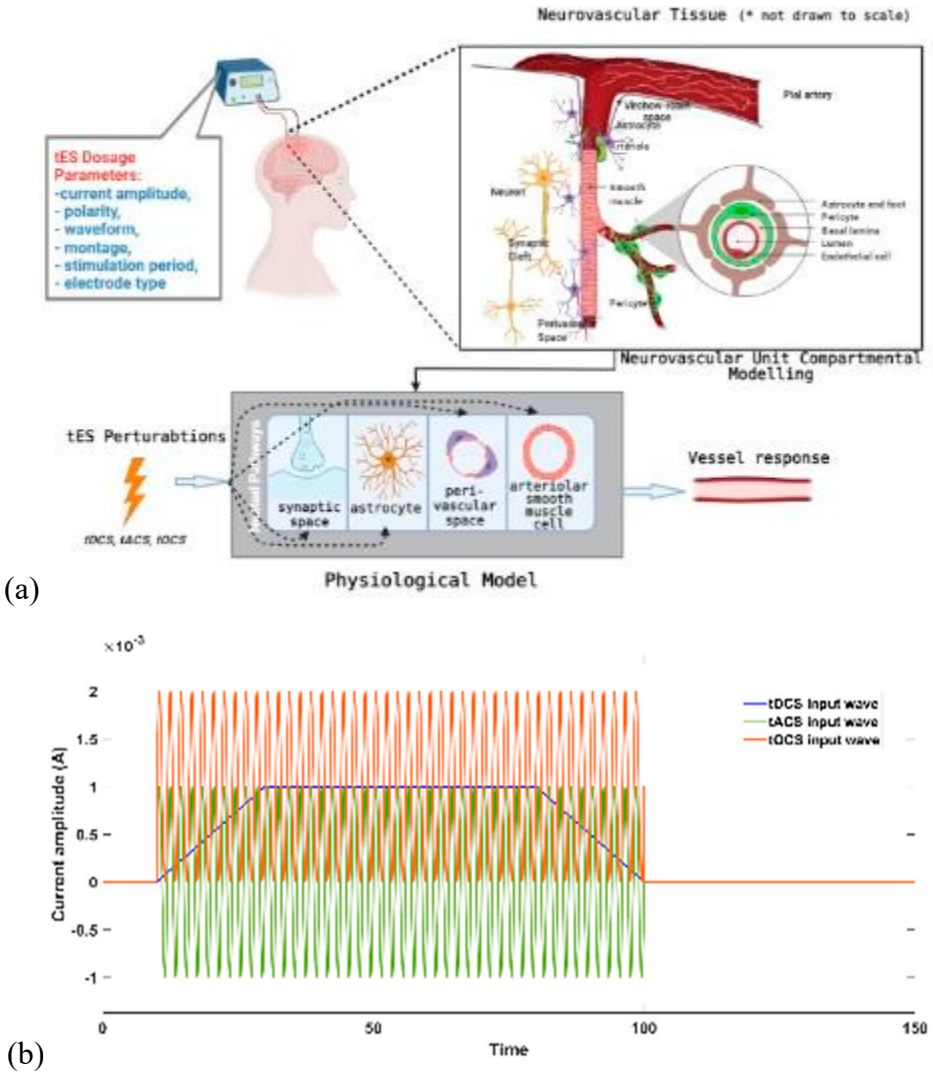

Figure 5. (a) Effect of tES dosage on neurovascular tissue: physiological modelling depiction. (b) tES timeseries perturbations for model evaluation. tDCS has a monophasic, non-oscillating baseline, while tACS rhythmically reverses electron flow. Additional methods include tOCS, guiding oscillations with a direct component, and tRNS, injecting bounded stochastic alternating current.

The major factors involved in the design of tES dosage are: current amplitude, waveform, polarity, duration, montage and electrode specifications (Knotkova et al., 2019) as depicted in Figure 5b. These factors are crucial in neuromodulating specific characteristics. For instance, tOCS has been shown to facilitate corticospinal excitability phase-independently both on and off-line, similar to tDCS (Bergmann et al., 2009). Meanwhile, tACS was more likely to entrain neuronal activity while blocking sensory input (Vieira et al., 2020). To comprehend the mechanistic aspects of tES techniques on hemodynamics, we used our mathematical model (Arora et al., 2021) based on the physiology of neurovascular tissue for evaluating the vascular response through various paths that are susceptible to the electric fields generated by tES as shown in Figure 5a. Our simulation model was constructed with four compartments, drawing from existing literature: synaptic space, astrocyte space, perivascular space, and arteriole smooth muscle cell space. To simulate the vessel volume response within the physiological model, we designed four nested neurovascular unit (NVU) compartmental pathways. Each state variable in these pathways could be influenced by the transcranial electrical stimulation (tES) current density, acting as the input pulse. The simulations of the model considered different tES-induced perturbations: synaptic potassium release from active neurons for Pathway 1, astrocytic transmembrane current for Pathway 2, perivascular potassium concentration for Pathway

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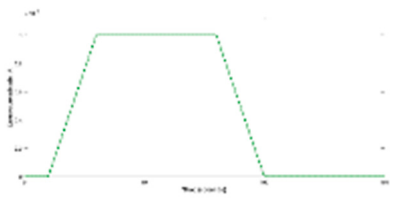
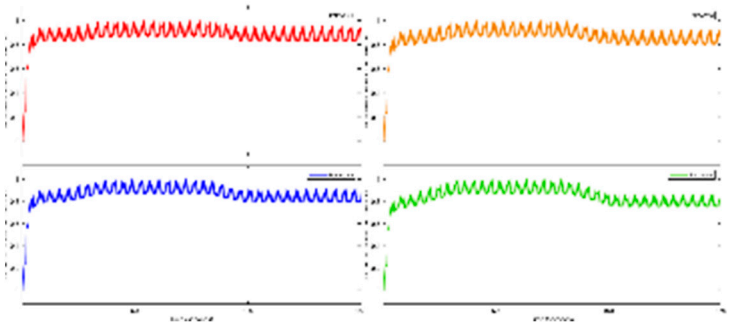
3, and voltage-gated ion channel current on the smooth muscle cells (SMC) for Pathway 4. Detailed information regarding the implementation and analysis can be found in the study (Arora et al., 2021).

Physiologically detailed models published earlier (Arora et al., 2021) were executed using the 'ode23tb' solver in Simulink (MathWorks, Inc., USA). These models simulated oscillations ranging from 0 to 0.2 Hz, generated by nonlinear calcium dynamics in response to transcranial direct current stimulation (tDCS) perturbations. Subsequently, we subjected the four nested neurovascular unit (NVU) compartmental pathways to perturbations from transcranial oscillating current stimulation (tOCS), tDCS, and transcranial alternating current stimulation (tACS) at varying frequencies (0.1 Hz to 10 Hz), conducting a sensitivity analysis for blood vessel diameter changes. Model simulations for different transcranial electrical stimulation (tES) pulses are available in supplementary material. This comprehensive approach considered the vascular effects of tES, incorporating both neuronal and non-neuronal mechanisms with distinct sensitivity levels. Notably, within the frequency range of 0.1 Hz to 10 Hz, we observed that vessel oscillations exhibited greater sensitivity to tOCS than to tACS, and entrainment effects were more pronounced at lower frequencies. Subsequently, modal analysis was performed on the physiological model, with detailed results presented in the following section.

Modal analysis of transcranial electrical stimulation effects on hemodynamics: We applied ten random transcranial electrical stimulation (tES) perturbations, utilizing bandpass filtered (0.01-1 Hz) white noise inputs, to the four implemented physiologically constrained models. The input and output time series were recorded using the time-domain data object ('iddata' in MATLAB, MathWorks, Inc., USA). For modal analysis, we focused on the oscillatory component of the vessel response, excluding the initial 50 seconds of time series data. Modal analysis functions, including 'modalfrf,' 'modalfit,' and 'modalsd,' were applied to the data object to generate frequency-response functions, natural frequencies, and stabilization diagrams, respectively. The natural frequencies of the four system modes, determined from the measured frequency-response functions (frf) at frequencies (f) and a sample rate of 10 samples per second, were calculated using the peak-picking method. The linear model of the four physiologically detailed tES perturbation pathways was established using the Model Linearizer tool in Simulink (MathWorks, Inc., USA) linear analysis package. The damping ratio, natural frequency, and time constant of the poles were derived using the 'damp' function on the linear model system.

The input of transcranial electrical stimulation (tES) and the corresponding vessel responses for the proposed pathways are detailed in Table 1. We subjected the four nested neurovascular unit (NVU) compartmental pathways to tOCS (combined tDCS and tACS) perturbations with varying frequencies (ranging from 0.1 Hz to 10 Hz) and direct current (DC) offsets (ranging from 0 to 2 mA). Subsequently, we conducted a sensitivity analysis to assess changes in blood vessel circumference.

Table 1. Model vessel response corresponding to tES input.

tES input	Vessel Response
 tDCS	

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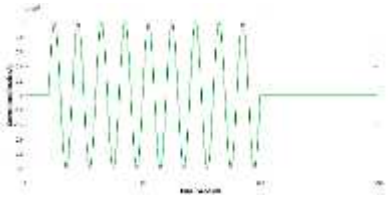
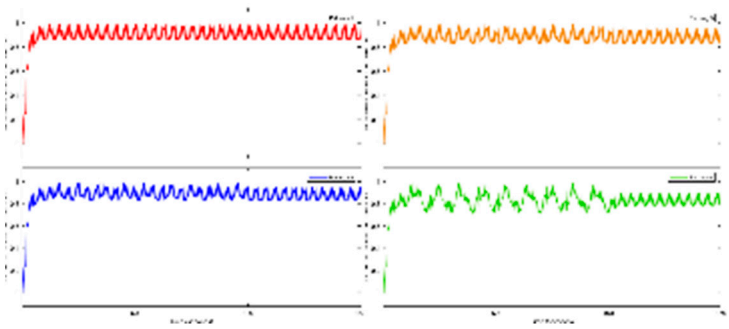
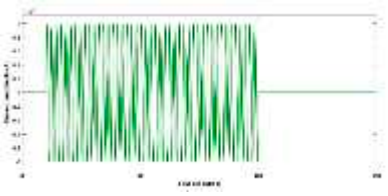
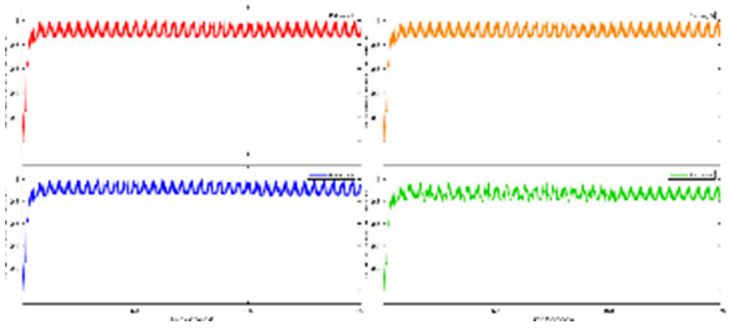
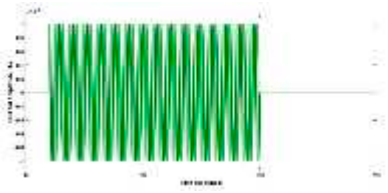
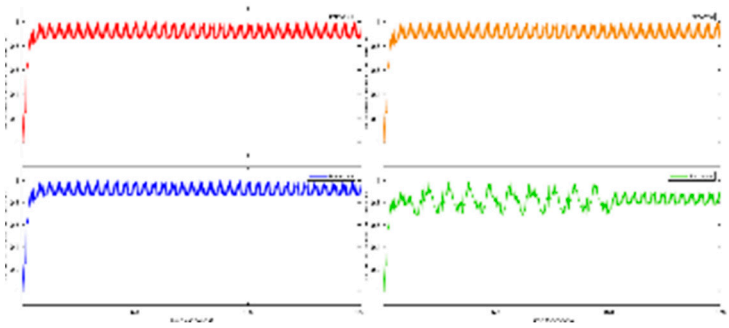
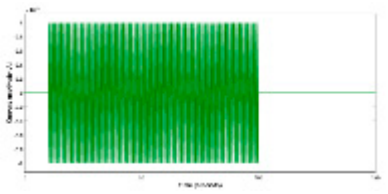
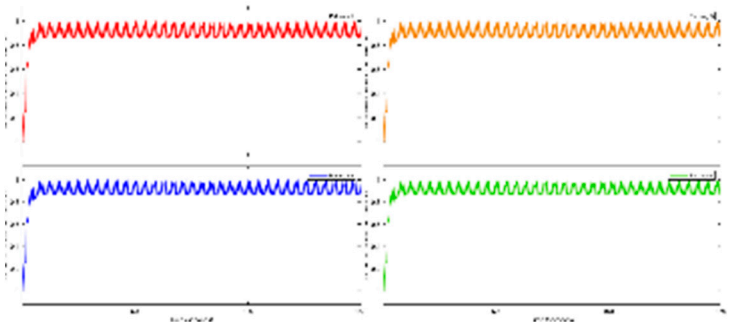
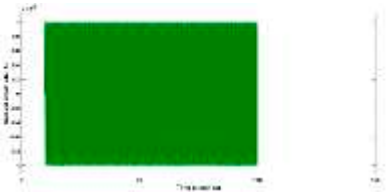
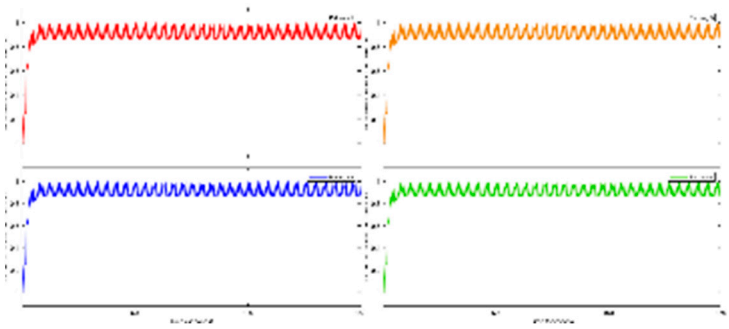
 tACS @ 0.1 Hz	
 tACS @ 0.5 Hz	
 tACS @ 1 Hz	
 tACS @ 5 Hz	
 tACS @ 10 Hz	

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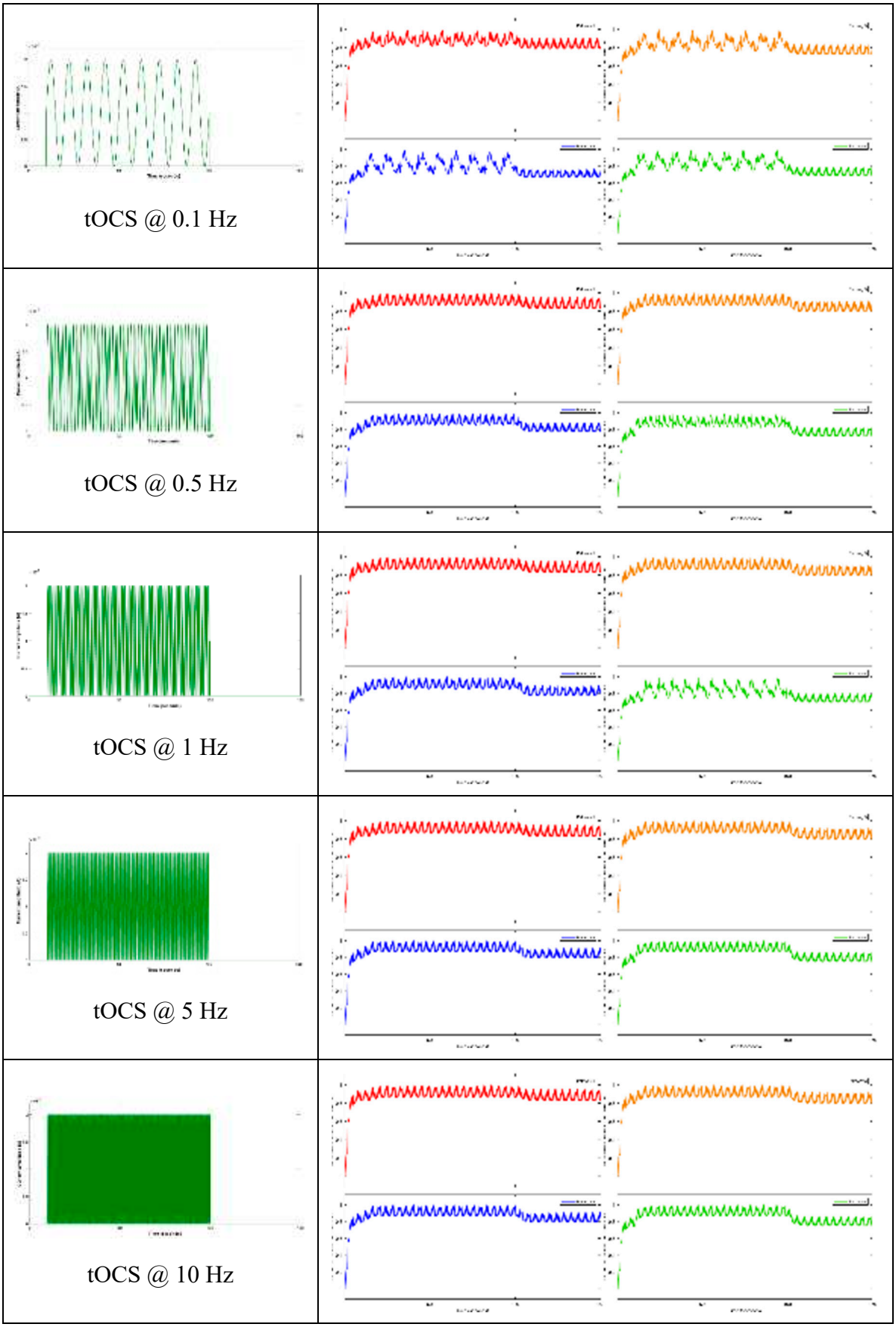

We considered three model input waveforms as

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$$\textbf{tES inputs}: \begin{cases} c \text{ for tDCS} \\ a\sin(2\pi ft) \text{ for tACS} \\ a\sin(2\pi ft) + c \text{ for tOCS} \end{cases} \quad (1)$$

In Equation (1), we considered a sinusoidal amplitude (a) of 1 mA, a sinusoidal frequency (f) ranging from 0.1 to 10 Hz, and a DC offset (c) ranging from 0 to 2 times the amplitude for conducting a sensitivity analysis on the physiologically detailed mathematical model of the neurovascular unit (NVU). This analysis, facilitated by the Sensitivity Analyzer tool in MATLAB Simulink (MathWorks, Inc., USA), enabled the exploration of the transcranial electrical stimulation (tES) design space, identifying the most influential model parameters. Figure 6 illustrates the impact of frequency and DC offset on the vessel response.

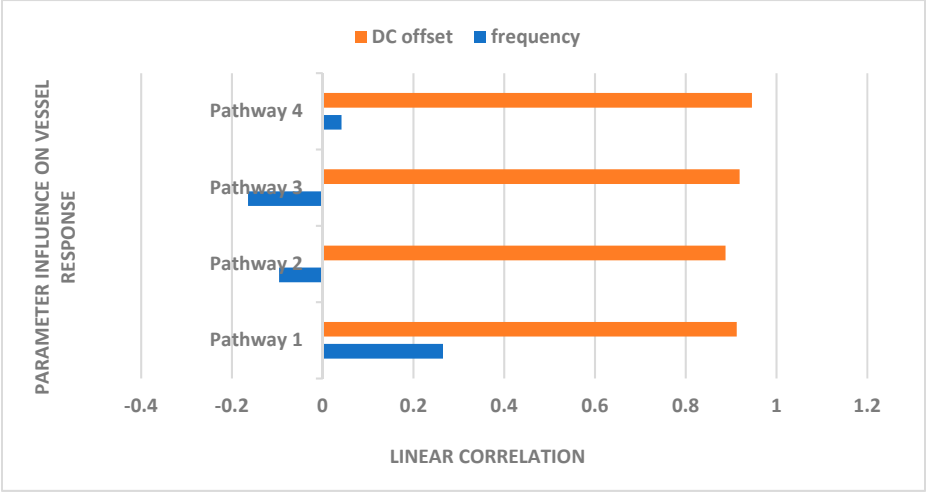

Figure 6. Effect of frequency (tDCS has frequency 0) and DC offset of tOCS on vessel circumference based on linear correlation for the proposed pathways.

Mechanistic Insights: Table 2 presents the natural frequencies derived through modal analysis for the non-linear models of four physiologically detailed transcranial electrical stimulation (tES) perturbation pathways. Figure 7 illustrates a boxplot representation of these frequencies. Additionally, Figure 8 displays the stabilization diagram obtained for the first case, where the model input was bandpass filtered white noise with the default seed value, for all four pathways. Then, Table 2 lists the system parameters associated with linearized model for the four pathways as follows. Pathway 1 involves tES perturbing the vessel response through the synaptic potassium pathway, Pathway 2 through the astrocytic pathway, Pathway 3 through the perivascular potassium pathway, and Pathway 4 through the smooth muscle cell (SMC) pathway.

Table 2. Natural frequencies obtained from the modal analysis (see also Figure 8) of the four physiologically detailed tES perturbation pathways (* default seed value).

Pathway / Bandpass filtered White Noise Input	P1 (K1 = 0.000001)	P2 (K2 = 0.00000000001)	P3 (K3 = 0.001)	P4 (K4 = 0.000000000001)

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1*	0.0000, , , 0.0193	, , , 0.0247	, 0.0052, 0.0157, 0.0265	0.0000, 0.0069, 0.0201,
2	, 0.0189, 0.0201,	0.0003, , 0.0156, 0.0167	0.0025, , 0.0231, 0.0235	, 0.0128, 0.0141,
3	0.0000, , 0.0153, 0.0195	0.0109, 0.0191, 0.0288, 0.0476	0.0027, 0.0081, 0.0196, 0.0236	0.0067, 0.0090, 0.0144,
4	, , 0.0115, 0.0245	, , ,	0.0050, , ,	0.0020, , 0.0168,
5	0.0007, 0.0077, 0.0200, 0.0276	, 0.0131, ,	0.0005, 0.0128, 0.0176,	, 0.0192, 0.0318,
6	0.0179, , 0.0363,	, , 0.0237, 0.0418	0.0055, , ,	, 0.0104, 0.0171,
7	, , 0.0107, 0.0131	0.0128, 0.0200, 0.0380, 0.0659	0.0036, , , 0.0386	, , , 0.0381
8	, 0.0225, 0.0298,	0.0048, 0.0100, ,	0.0011, , 0.0209,	0.0043, 0.0223, ,
9	0.0000, , , 0.0215	0.0038, , 0.0285,	0.0033, 0.0083, , 0.0184	, 0.0099, 0.0164,
10	, 0.0198, 0.0319, 0.0360	, 0.0189, 0.0229, 0.0242	, 0.0058, , 0.0188	, , , 0.0387

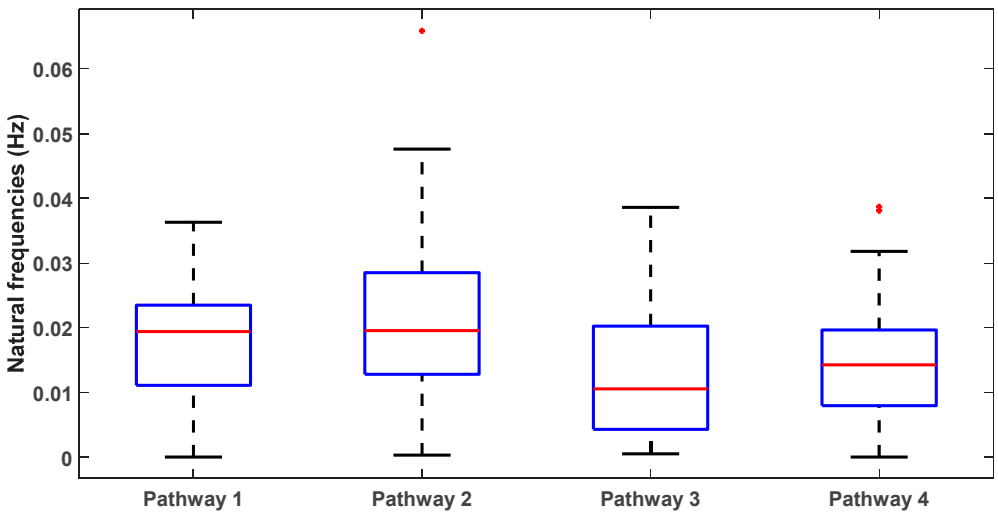

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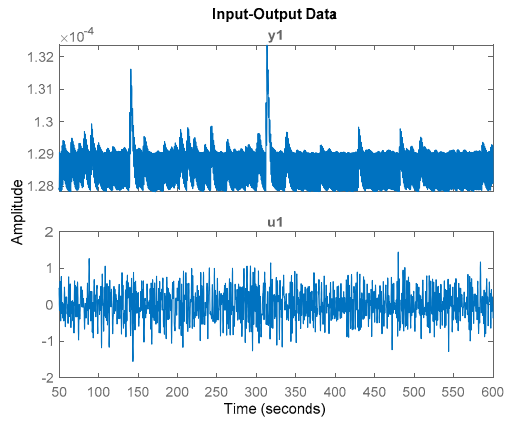
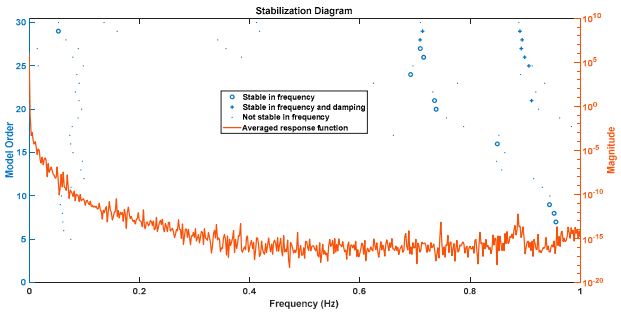
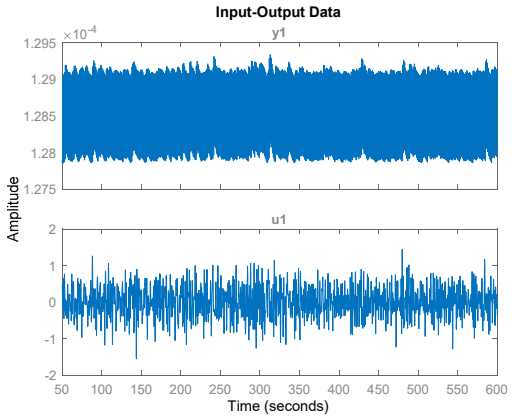
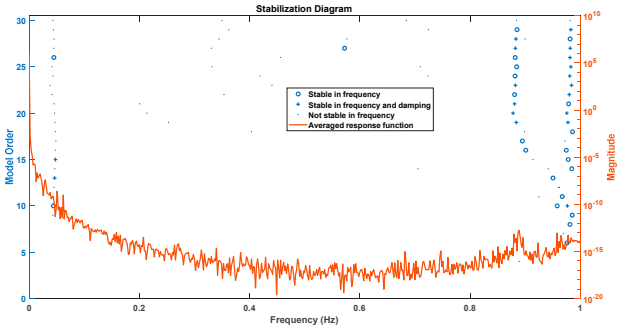
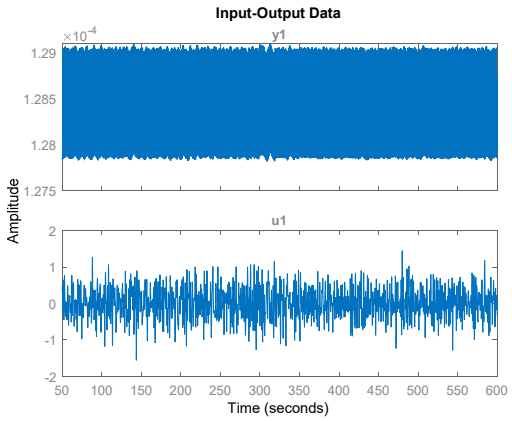
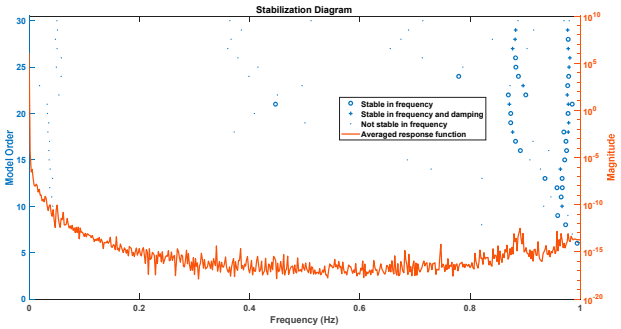
Figure 7. The boxplot illustrates the distribution of natural frequencies resulting from modal analysis for the four transcranial electrical stimulation (tES) perturbation model pathways. Each box represents the interquartile range, with the central mark denoting the median. The bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Whiskers extend to the most extreme data points that are not considered outliers, while outliers are individually marked with a red '+' symbol.

Input (u1)-Output (y1)	Stabilization Diagram
Pathway 1	
	
Pathway 2	
	
Pathway 3	
	

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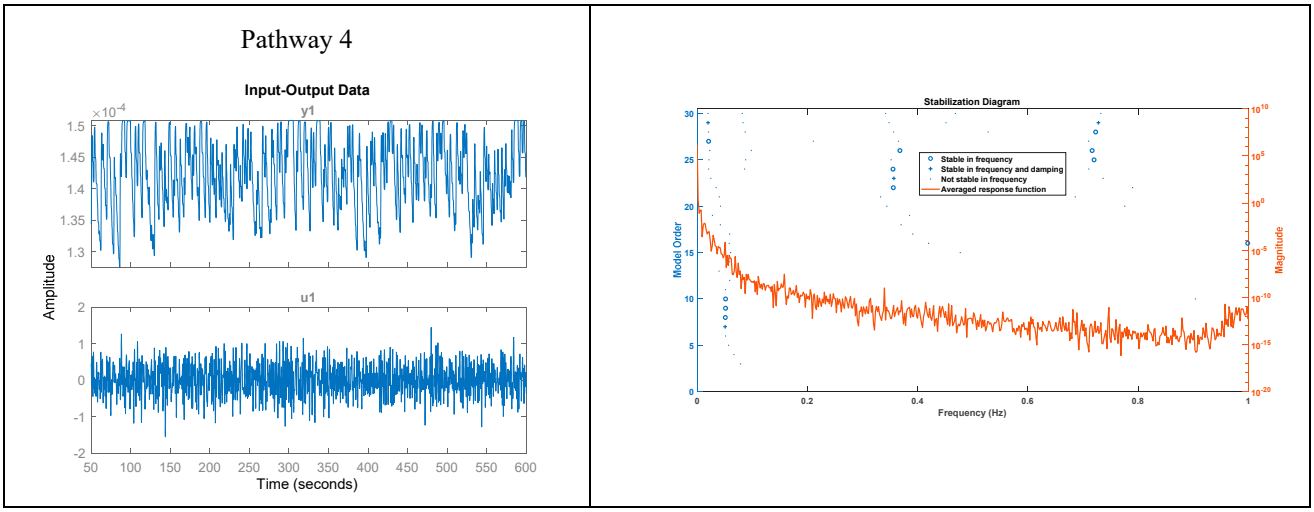

Figure 8. Stabilization diagram obtained for the first case (model input: bandpass filtered white noise, default seed value) for the four pathways.

Table 3. System characteristics for the four linearized model pathways.

Pathway	Poles	Damping	Frequency (rad/seconds)	Time constant (seconds)
1	-2.45e-01, -4.00e-01, -1.00e+00, -1.97e+00, -3.30e+00, -4.90e+00 + 8.44e+00i, -4.90e+00 - 8.44e+00i, -1.51e+01, -2.07e+01, -2.97e+04, -9.59e+06	1.00e+00, 1.00e+00, 1.00e+00, 1.00e+00, 1.00e+00, 5.02e-01, 5.02e-01, 1.00e+00, 1.00e+00, 1.00e+00, 1.00e+00,	2.45e-01, 4.00e-01, 1.00e+00, 1.97e+00, 3.30e+00, 9.76e+00, 9.76e+00, 1.51e+01, 2.07e+01, 2.97e+04, 9.59e+06	4.09e+00, 2.50e+00, 1.00e+00, 5.09e-01, 3.03e-01, 2.04e-01, 2.04e-01, 6.63e-02, 4.83e-02, 3.36e-05, 1.04e-07
2	-2.45e-01, -1.00e+00, -1.97e+00, -3.30e+00, -4.90e+00 + 8.44e+00i,	1.00e+00, 1.00e+00, 1.00e+00, 1.00e+00, 5.02e-01,	2.45e-01, 1.00e+00, 1.97e+00, 3.30e+00, 9.76e+00,	4.09e+00, 1.00e+00, 5.09e-01, 3.03e-01, 2.04e-01,

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	-4.90e+00 - 8.44e+00i, -1.51e+01, -2.07e+01, -2.97e+04, -9.59e+06	5.02e-01, 1.00e+00, 1.00e+00, 1.00e+00, 1.00e+00,	9.76e+00, 1.51e+01, 2.07e+01, 2.97e+04, 9.59e+06	2.04e-01, 6.63e-02, 4.83e-02, 3.36e-05, 1.04e-07
	-2.45e-01, -1.00e+00, -3.30e+00, -4.90e+00 + 8.44e+00i, -4.90e+00 - 8.44e+00i, -2.07e+01, -2.97e+04, -9.59e+06	1.00e+00, 1.00e+00, 1.00e+00, 5.02e-01, 5.02e-01, 1.00e+00, 1.00e+00, 1.00e+00,	2.45e-01, 1.00e+00, 3.30e+00, 9.76e+00, 9.76e+00, 2.07e+01, 2.97e+04, 9.59e+06	4.09e+00, 1.00e+00, 3.03e-01, 2.04e-01, 2.04e-01, 4.83e-02, 3.36e-05, 1.04e-07
4	-2.45e-01, -3.30e+00, -4.90e+00 + 8.44e+00i, -4.90e+00 - 8.44e+00i, -2.07e+01, -9.59e+06	1.00e+00, 1.00e+00, 5.02e-01, 5.02e-01, 1.00e+00, 1.00e+00,	2.45e-01, 3.30e+00, 9.76e+00, 9.76e+00, 2.07e+01, 9.59e+06	4.09e+00, 3.03e-01, 2.04e-01, 2.04e-01, 4.83e-02, 1.04e-07

Discussion on tES implications in type 2 Diabetes and dementia (by Anirban Dutta)

The relationship between baroreflex sensitivity, cerebral neuronal fiber integrity, and aortic stiffness in T2DM with normal cognitive function versus amnestic Mild Cognitive Impairment (MCI), a precursor to Alzheimer's disease, needs investigation. Using cardiovascular and neuroimaging assessments, prior work (Tarumi et al., 2015) found that lower fractional anisotropy (FA) and higher radial diffusivity (RD) were associated with reduced baroreflex sensitivity and poorer executive function in older adults; however, the neurovascular coupling status was not investigated. Nevertheless, prior work (Tarumi et al., 2015) suggests a potential link between impaired baroreflex-mediated blood pressure regulation, particularly during hypotension, and negative effects on brain structures, highlighting the baroreflex as a cardiovascular marker for identifying T2DM individuals at an elevated risk of cognitive impairment. Our clinical studies (Zhao et al., 2023),(Dutta et al., 2021) showcased the positive impacts of a personalized, two-month progressive exercise regimen on cognitive function and muscular oxidative capacity in older adults diagnosed with T2DM which may be subserved by a decrease in hormonal stress, postulated based on operational modal analysis of fNIRS measures (Zhao et al., 2023), that needs to be evidenced by lower plasma norepinephrine concentrations in future studies as observed at submaximal work intensities in prior findings (Tyni-Lenné et al., 1998). In Figure 3d versus 3e, we show that our exercise intervention led to a diminished

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surge in oxyhemoglobin concentration changes during medium-difficulty cognitive tasks, suggesting a potential improvement in systemic blood pressure regulation via the arterial baroreflex (Ogoh and Tarumi, 2019). Then, in individuals over 60, tDCS has been shown to induce cardiovascular and autonomic improvements, enhancing ventricular repolarization dispersion timing, decreasing sympathetic activity and peripheral resistance, and increasing vagal sinus activity and baroreflex sensitivity (Piccirillo et al., 2016). Although the authors (Piccirillo et al., 2016) hypothesized that the anodal tDCS effects on the neuronal networks in the temporal cortex and insular cortex are linked to autonomic nervous system regulation and the perception of emotional sensations within the body, they did not show the effects of anodal tDCS on unrelated brain areas and so the mechanism of action is unclear. Figure 5a outlines our proposed mechanism through which tES influences the perivascular space, as theorized by Arora et al. (Arora et al., 2021). The hypothesis posits that tES modulates the vasculature via the perivascular pathway, leading to vasoconstriction increasing and vasodilation decreasing the perivascular space volume, as depicted in Figure 1a. In a computational model (Arora et al., 2021), an immediate vascular response was captured through the perivascular pathway, involving the interaction between perivascular potassium and calcium concentrations, resulting in steady-state vessel oscillations below 0.1 Hz. These oscillations may potentially synchronize with neuronal oscillations, enabling the exploration of neurovascular coupling through joint imaging with fNIRS-EEG (Sood et al., 2016). Acute tES within a short duration (<150 sec), as indicated by Arora et al. (Arora et al., 2021), can impact the vasculature for immediate control of blood vessel response using model predictive control (MPC) (Arora and Dutta, 2022). MPC employs an internal model that considers cortical activity, local metabolic factors, and vascular response to optimize tES control actions over a predefined prediction horizon, operating in a receding horizon fashion for online operation. Then, rapid vascular response observed at the onset of tES (Arora et al., 2021) could modulate bulk flow of cerebrospinal fluid (Faghih and Sharp, 2018) when applied as slow oscillations according to the resonance frequencies (see Figure 8), creating an opportunity for human-in-the-loop optimization based on blood volume (total hemoglobin) feedback from fNIRS (Arora and Dutta, 2022). Previous research (Arora and Dutta, 2022) utilizing modal analysis and a case study in a healthy human suggested that an "optimal" oscillatory frequency, approximately 1 Hz, warrants further investigation on the effects of bulk flow of cerebrospinal fluid (Faghih and Sharp, 2018) vis-à-vis the state of the astrocytes, extracellular glucose (Silver and Erecińska, 1994), and interstitial potassium (tES modulation of neurovascular coupling? (Dutta, 2021b)). Our hypothesis suggests the presence of an optimal transcranial electrical stimulation (tES) oscillatory pattern could offer therapeutic benefits for acute effects on the vasculature and/or astrocyte end feet (Arora and Dutta, 2022). Then, the distribution of natural frequencies (see Figure 7) has the potential to modulate slow oscillations <0.05Hz (Zhao et al., 2023) that are often decreased in type 2 diabetes as highlighted in our prior works (Zhao et al., 2023),(Zhao et al., 2022) – see Figure 9. However, we need to be careful with the interpretation where findings suggest that the existence T2DM does not elevate the pace of cognitive deterioration in Alzheimer's Disease (Davidson et al., 2023). This discovery challenges anticipated disease impact and warrants investigation into the brain-behaviour effects in T2DM such as exercise intolerance and sedentary behaviour that subserves cognitive deterioration primarily in the MCI stage of the Alzheimer's Disease.

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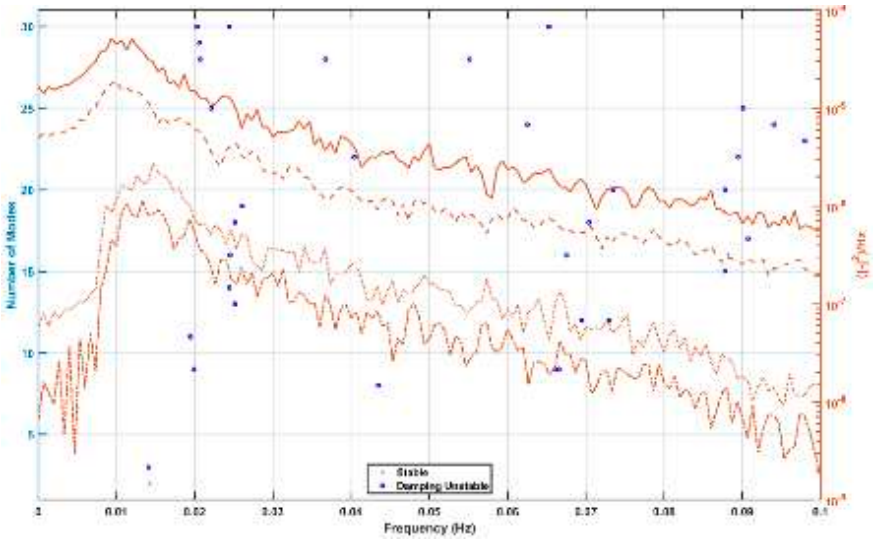

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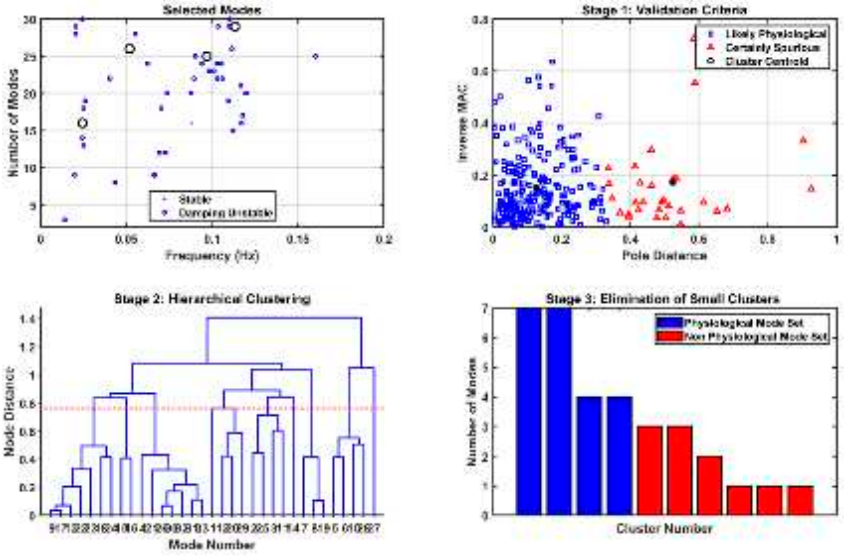

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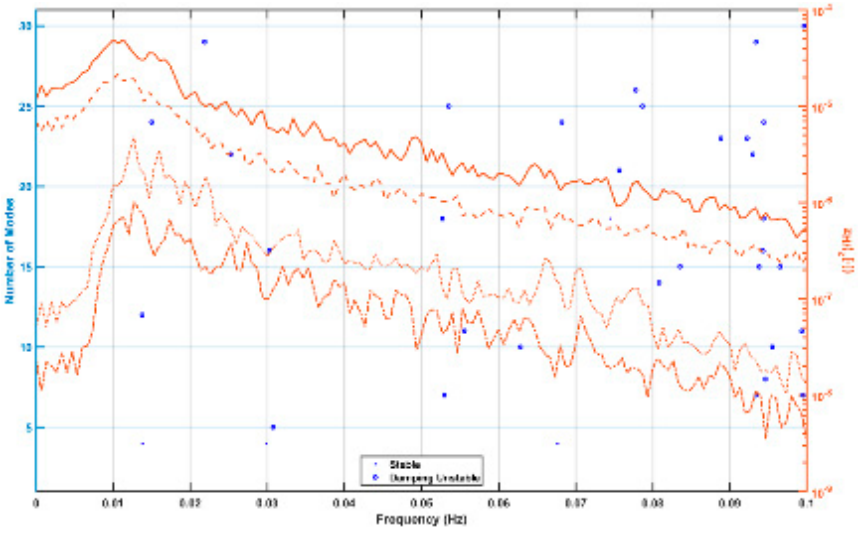

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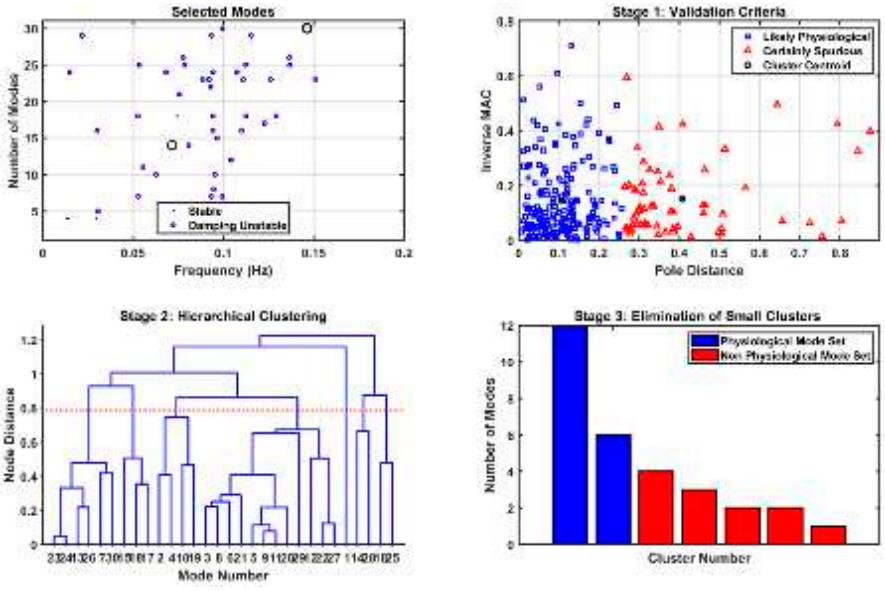

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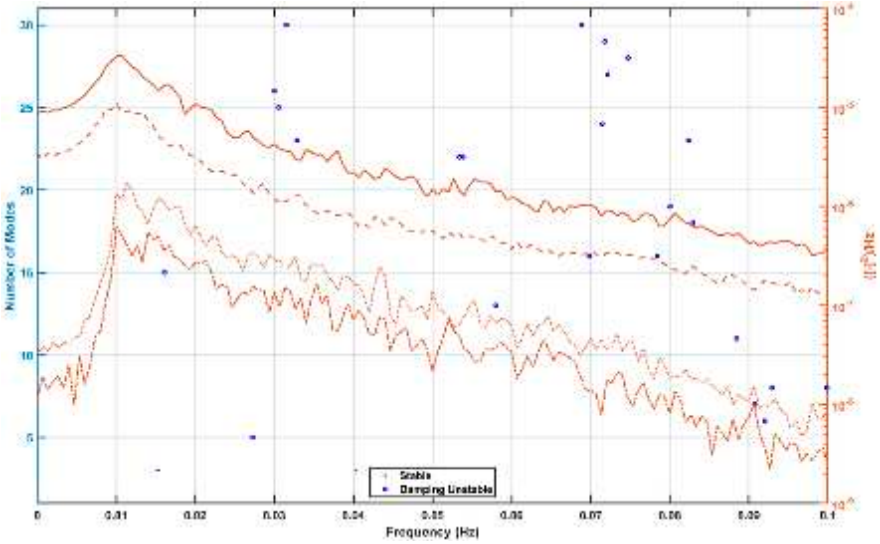

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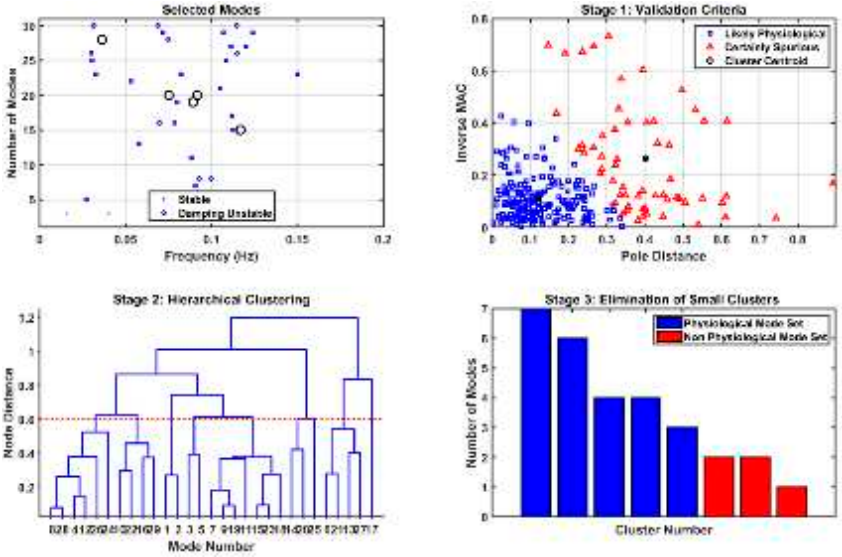

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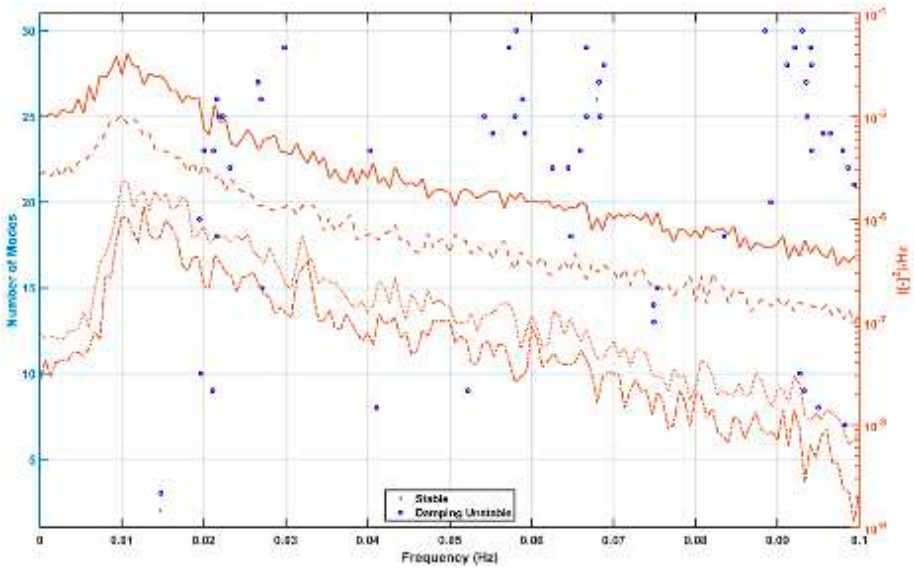

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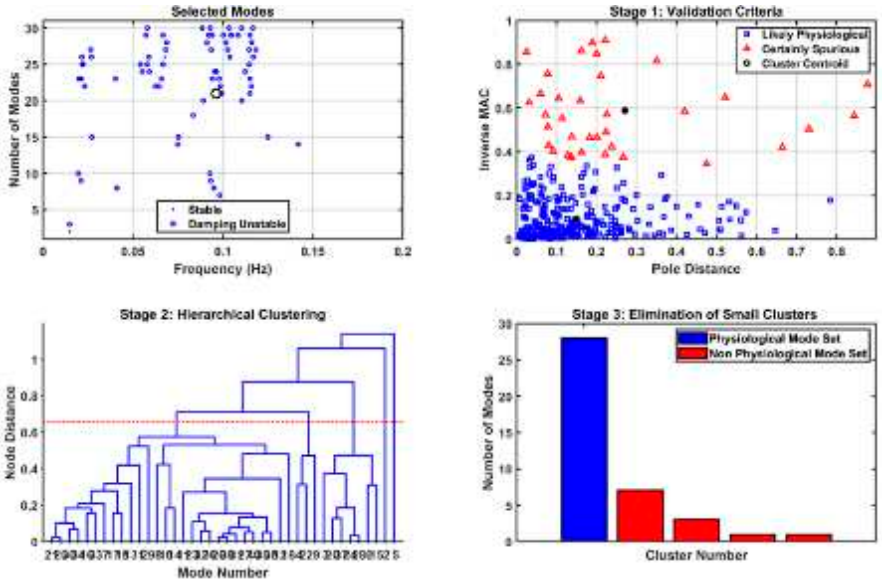

Figure 9. Operational modal analysis (OMA) was conducted on near-infrared spectroscopy effects, considering a maximum of 30 modes for the power spectrum <0.1Hz, as depicted in the stabilization diagram. Subsequently, a multi-stage clustering approach was employed to identify physiological clusters, utilizing the Modal Toolkit available at https://code.vt.edu/vibes-lab/modal-analysis. Figures A1 and B1 represent the stabilization diagram and the multi-stage clustering, respectively, for the Sedentary healthy control group. Similarly, A2 and B2 illustrate the stabilization diagram and multi-stage clustering for the Active healthy control group. A3 and B3 present the stabilization diagram and multi-stage clustering for the T2DM intervention group pre-intervention, while A4 and B4 depict the stabilization diagram and multi-stage clustering for the T2DM intervention group post-intervention. (from (Zhao et al., 2023)).

Recent findings by Minager et al. (https://www.ismrm.org/workshops/2022/Neuromodulation/program.php) provide support for the immediate alteration of perivascular space morphology by tES that may be linked to the vascular response (Arora and Dutta, 2022),(Arora et al., 2021). With the convenience of neuroimaging in a point-of-care setting compared to MRI-tES, the portable neuroimaging-based Model Predictive Control (MPC) of tES (Arora and Dutta, 2022) can also be applied during sleep to facilitate glymphatic clearance (Kim et al., 2018). This innovative approach enables the optimization of tES patterns at the point of care to elicit the required blood volume response, potentially reducing risks associated with

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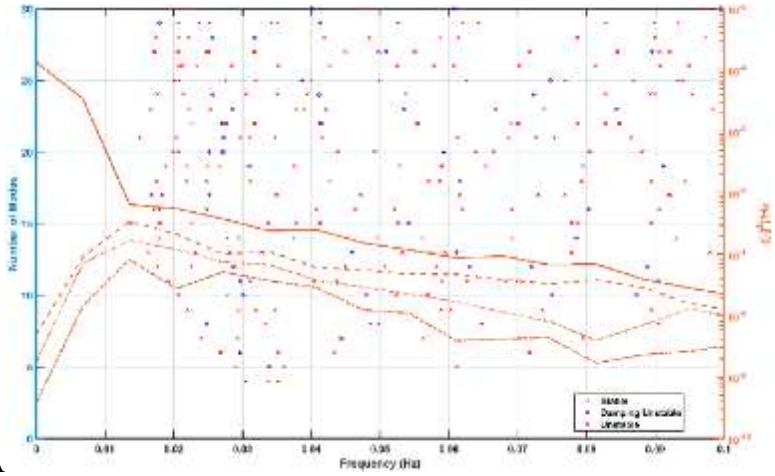
heightened metabolic demand in pathological tissues, such as ischemia in vascular dementia. The authors posit that the therapeutic use of tES might transform the neurovascular unit due to bulk flow of cerebrospinal fluid, enhancing its sensitivity for favourable cognitive outcomes (Dutta, 2021a), such as diminished cognitive fatigue (Wiehler et al., 2022), attributed to improved extracellular clearance. Nevertheless, we need to be aware of the limitations where task and stimulus related systemic effects (Tachtsidis and Scholkmann, 2016), i.e., cerebral and muscle metaboreflex including changes in the blood pressure, heart rate, arousal, etc. may not be limited to superficial tissues (addressed with short separation regression in the time domain (Yücel et al., 2015)) but may have an effect on the neurovascular response itself due to the interacting pathways shown in our prior works (Arora et al., 2021),(Arora and Dutta, 2022). Here, separation in the frequency domain may be more fruitful especially when oscillatory modes are different as found from the modal analysis presented in our prior works (see multi-stage clustering in (Zhao et al., 2023)) – see Figure 10. This needs future investigation for validation.

A



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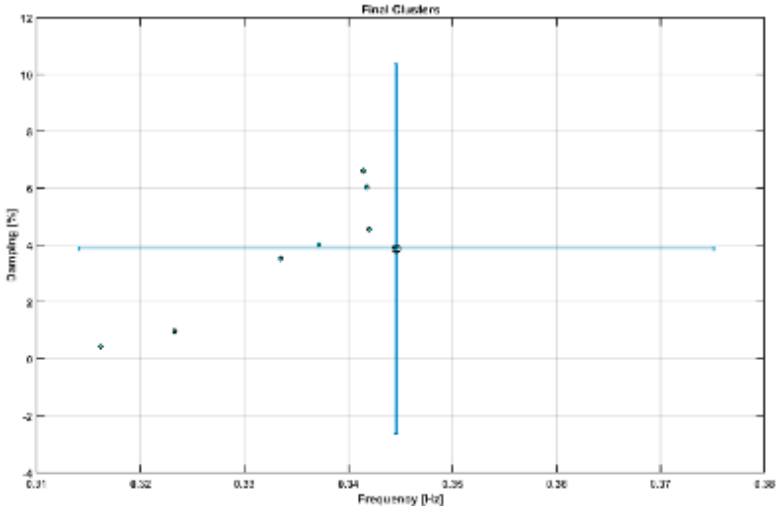

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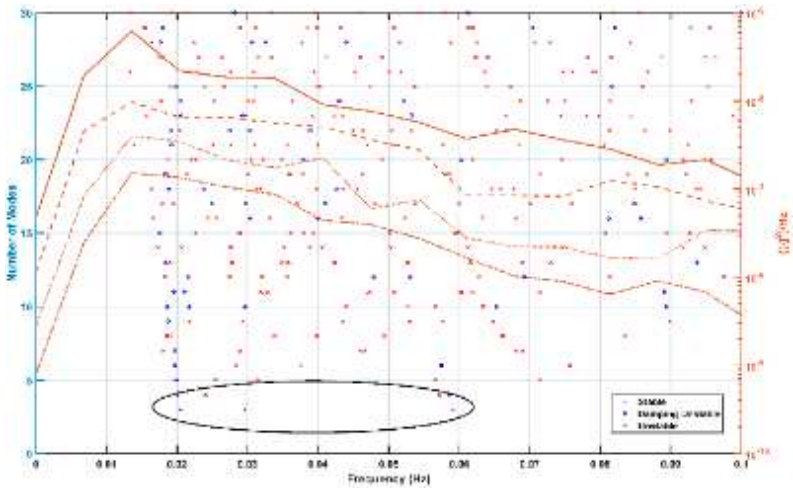

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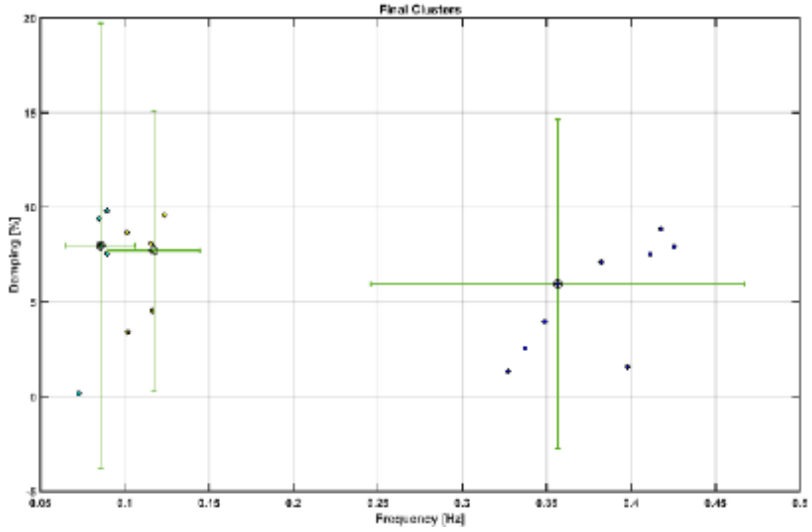

Figure 10. Operational Modal Analysis (OMA) was performed on near-infrared spectroscopy signals obtained from both long-separation and short-separation channels, allowing for a maximum of 30 modes within the power spectrum <0.1Hz. The resulting stabilization diagram is presented for healthy control subjects (N=10), followed by a multi-stage clustering process to identify physiological clusters, employing the Modal Toolkit (https://code.vt.edu/vibes-lab/modal-analysis). A. Stabilization diagram for the short-separation near-infrared spectroscopy channels, B. Multi-stage clustering for the short-separation near-infrared spectroscopy channels. C. Stabilization diagram for the long-separation near-infrared spectroscopy channels, D. Multi-stage clustering for the long-separation near-infrared spectroscopy channels. (from (Zhao et al., 2023)).

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