The use of non-invasive brain stimulation to modulate beta waves during movement of the hand in elderly and stroke individuals

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ABSTRACT

Aging is characterized by a deterioration in reaction time, motor coordination, and motor learning. Previous studies using electroencephalography (EEG) in elderly individuals have shown abnormalities in movement-related beta desynchronization (MRBD) patterns. Some studies also used methods to alter these patterns using non-invasive brain stimulation (NIBS) techniques such as transcranial alternating current stimulation (tACS). Recent studies have revealed the existence of high amplitude transient bursts that might be at the origin of sustained beta oscillatory activity patterns in the motor cortex such as the MRBD and are denoted as beta bursts. However, beta bursts have not been studied as extensively as MRBD. The objectives of this thesis were to determine the link between beta burst characteristics (rate, amplitude, duration) and previously described beta power analysis on the same subjects, as well as quantify the long-term effects of 20Hz and 70Hz high-definition (HD) tACS on beta bursts in elderly individuals.

The current single-blinded sham-controlled study involved 15 healthy elderly participants. In three different experimental sessions, three different HD-tACS protocols (20Hz, 70Hz, sham) were applied over the left sensorimotor cortex while participants performed a motor handgrip task with their right hand. The subjects had their brain activity recorded using EEG while at rest and while performing the above-mentioned motor task before the stimulation, 15 minutes post-stimulation, and 45 minutes post-stimulation. Brain activity was also recorded during the stimulation block. Our results show that both burst rate and burst amplitude were lower during the movement interval compared to pre-movement and post-movement, which was similar to the MRBD patterns obtained using power analysis, which showed a decrease in beta power during movement followed by an increase in beta power upon movement termination. This pattern was more evident in burst amplitude than burst rate. When looking at the effects of stimulation over

time, it was observed that 20Hz stimulation caused an increase in burst amplitude 15 minutes post-stimulation during the post-movement interval, while 70Hz stimulation caused an increase in burst amplitude 45 minutes post-stimulation during the movement interval. No effects of stimulation were observed for burst rate and burst duration. There was no clear association between any of the burst characteristics and the results obtained from beta power analysis in the context of stimulation.

An exploratory analysis was performed on an initial stroke dataset that had an almost identical experimental protocol to the elderly study. Preliminary results show that stroke survivors have a much lower overall absolute beta power and lower burst rate and amplitude compared to healthy elderly individuals.

The findings of this study shed light on the association between beta bursts and MRBD, as well as on the long-term effects of 20Hz and 70Hz tACS stimulation on different burst characteristics. Ultimately, this study will contribute to our long-term goal of developing targeted stimulation protocols based on each individual's brain activity.

RÉSUMÉ

Le vieillissement se caractérise par une détérioration du temps de réaction, de la coordination motrice et de l'apprentissage moteur. Des études antérieures utilisant l'électroencéphalographie (EEG) chez des personnes âgées ont montré des anomalies dans les valeurs de la désynchronisation bêta liée au mouvement (MRBD). En outre, ces valeurs peuvent être modifiés par des techniques de stimulation cérébrale non invasives (NIBS) telles que la stimulation transcrânienne à courant alternatif (tACS). Des études récentes ont révélé l'existence de rafales transitoires à haute amplitude qui pourraient être à l'origine de l'activité oscillatoire soutenue bêta dans le cortex moteur comme la MRBD et sont appelées des rafales bêta. Cependant, les rafales bêta n'ont pas été étudiées de manière aussi approfondie que la MRBD. Les objectifs de cette thèse étaient de déterminer le lien entre les caractéristiques des rafales bêta (fréquence, amplitude, durée) et la puissance bêta précédemment analysée sur les mêmes sujets, ainsi que de quantifier les effets à long terme de la tACS haute définition (HD) à 20Hz et 70Hz sur les rafales bêta chez les personnes âgées.

L'étude actuelle a impliqué 15 participants âgés en bonne santé. Lors de chacune des trois sessions expérimentales, un protocole HD-tACS différent (20Hz, 70Hz, placebo) a été appliqué sur le cortex sensorimoteur gauche pendant que les participants effectuaient une tâche motrice de préhension avec leur main droite. L'activité cérébrale des sujets a été enregistrée par EEG au repos et pendant l'exécution de la tâche motrice susmentionnée avant la stimulation, 15 minutes après la stimulation et 45 minutes après la stimulation. Nos résultats ont montré que la fréquence et l'amplitude des rafales ont été plus faibles pendant l'intervalle de mouvement qu'avant et après le mouvement, ce qui a été similaire au MRBD obtenue par l'analyse de puissance bêta qui montre une diminution de la puissance bêta pendant le mouvement suivi d'une augmentation de la

puissance bêta à la fin du mouvement. Cette similarité a été plus évidente dans l'amplitude des rafales que dans la fréquence de rafales. Lorsque l'on a examiné les effets de la stimulation dans le temps, on a constaté que la stimulation à 20 Hz a entraîné une augmentation de l'amplitude des rafales 15 minutes après la stimulation pendant l'intervalle après le mouvement, tandis que la stimulation à 70 Hz a entraîné une augmentation de l'amplitude des rafales 45 minutes après la stimulation pendant l'intervalle de mouvement. Aucun effet de la stimulation n'a été observé pour la fréquence et la durée des rafales. Il n'y a pas eu d'association claire entre les caractéristiques des rafales et les résultats obtenus par l'analyse de la puissance bêta dans le contexte de la stimulation.

Une analyse exploratoire a été effectuée sur un ensemble de données initial sur des personnes qui ont subi un AVC dont le protocole expérimental était presque identique à celui de l'étude sur les personnes âgées. Les résultats préliminaires montrent que les survivants d'AVC ont une puissance bêta absolue globale beaucoup plus faible et une fréquence et amplitude de rafales bêta plus faibles que les personnes âgées en bonne santé.

Les résultats de cette étude mettent en lumière la relation entre les rafales bêta et la MRBD, ainsi que les effets à long terme de la tACS à 20Hz et 70Hz sur les différentes caractéristiques des rafales. En fin de compte, cette étude contribuera à notre objectif à long terme de développer des protocoles de stimulation personnalisés basés sur l'activité cérébrale de chaque individu.

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CONTRIBUTION OF AUTHORS

The contribution of authors is as follows:

George Lungoci recruited and conducted the data collection on the ongoing stroke dataset and helped in the data collection for the elderly dataset. He performed the beta burst analysis on both the elderly and stroke datasets and the beta power analysis on the stroke dataset. He also performed the statistical analyses and plotted all the figures and graphs in this thesis. Finally, he wrote the manuscript for this thesis.

Dr. Marie-Hélène Boudrias is my thesis supervisor and provided support in all the steps leading to writing this thesis. More specifically, she provided the study design and helped in the data collection in both the stroke and elderly datasets. She also provided feedback on the various analyses conducted, including the figures and tables to be used in this thesis. She also helped proofread the manuscript of the thesis.

Kenya Morales Fajardo conducted the data collection on the elderly dataset and performed part of the preprocessing for both the elderly and stroke datasets. She also helps in the current recruitment and data collection for stroke participants.

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LIST OF ABBREVIATIONS

9HPT: Nine Hole Peg Test

BBT: Box and Block Test

CNS: Central Nervous System

CS: Corticospinal

CT: Computer Tomography

EEG: Electroencephalography

FMA-UL: Fugl-Meyer Assessment – Upper Limb

fMRI: Functional Magnetic Resonance Imaging

HD: High Definition

HGS: Handgrip Strength

Hz: Hertz

ICA: Independent Component Analysis

kΩ: Kiloohms

M1: Primary Motor Cortex

mA: Milliamps

MEG: Magnetoencephalography

min: Minutes

MRBD: Movement-Related Beta Desynchronization

MRI: Magnetic Resonance Imaging

ms: Milliseconds

MVC: Maximum Voluntary Contraction

NIBS: Non-Invasive Brain Stimulation

PET: Positron Emitted Tomography

PMBR: Post-Movement Beta Rebound

PPT: Purdue Pegboard Test

pV: Picovolts

ROI: Region Of Interest

s/sec: Seconds

SMA: Supplementary Motor Area

tACS: Transcranial Alternating Current Stimulation

tDCS: Transcranial Direct Current Stimulation

tES: Transcranial Electrical Stimulation

TF: Time-Frequency

µV: Microvolts

CHAPTER 1: INTRODUCTION

1.1 Statement of Problem

Electroencephalography (EEG) is widely used in research to record brain activity and extract relevant oscillatory patterns such as those in the beta frequency range (15Hz-29Hz) relevant to movement. One such pattern that has been extensively used in research is movement-related beta desynchronization (MRBD), defined as a decrease in the beta spectral power of brain waves during movement production. The pattern of MRBD activity has been shown to change with aging and in stroke and these changes have been associated with decreased motor performance. One method capable of influencing and normalizing these abnormal brain activities is non-invasive brain stimulation (NIBS). A common NIBS tool used extensively in research is transcranial alternating current stimulation (tACS), a technology capable of passing weak sinusoidal current through the scalp and entraining brain oscillations at specific rhythms. A recent study in our lab showed that 20Hz & 70Hz tACS stimulation protocols can have different long-term effects on the MRBD patterns in elderly subjects (Morales Fajardo, 2023).

Recent studies have revealed the existence of high amplitude transient bursts that might be at the origin of sustained beta oscillatory activity in the motor cortex such as the MRBD and are denoted as beta bursts. However, to our knowledge, few studies have looked at the association between beta bursts and MRBD, and no studies have examined the effects of NIBS on beta bursts in elderly individuals and stroke survivors. It is thus crucial to better understand the brain mechanisms of movement production and find alternative rehabilitation techniques to reduce motor impairment in these individuals. One such technique is proposed in this study, and it involves using both EEG and high-definition (HD)-NIBS to record and modulate the cortical

activity in the motor cortex of elderly and stroke subjects in order to better understand the long-term effects of stimulation on beta bursts.

1.2 Background

1.2.1 Aging

The Canadian population is drastically increasing in age such that the senior population aged 65 or more is estimated to grow by 68% by 2037 (*Infographic: Canada's seniors population outlook: Uncharted territory*, 2017). Aging is characterized by several transformations, including physical, psychological, and social.

It has been well documented that the brain becomes increasingly atrophied in several regions with age. While a great amount of atrophy has been observed in the prefrontal cortex (Raz *et al.*, 2004), an area important in processing and regulating behavior and emotions (Miller & Cohen, 2001), brain areas important in motor function also present significant volume atrophy. Such areas are the caudate nucleus, cerebellum, and the sensorimotor cortical regions (Ivry *et al*., 2002; Raz *et al*., 2005; Taubert *et al*., 2020). It is thus not unexpected that elderly individuals show a deterioration in reaction time, motor coordination, and motor learning (Smith *et al.*, 1999). Furthermore, this decline in motor function may seriously affect their quality of life (Paskulin *et al.*, 2007). That is why it is important to understand how these changes occur and hopefully find methods to counter this deterioration.

1.2.2 Stroke

Stroke is a debilitating neurological condition which is the third leading cause of death in Canada (*Statistics Canada*, 2017), and where survivors often experience profound physical and cognitive disabilities. More than 700,000 Canadian stroke survivors are recorded yearly (*Government of Canada*, 2017), of which 400,000-500,000 of them suffer from complications,

present significant disabilities, and 40% need assistance in their daily activities (*Government of Canada*, 2009; Hankey *et al.*, 2002; *Heart and Stroke Foundation of Canada*, 2017).

There are two main types of strokes: ischemic and hemorrhagic. Ischemic stroke is caused by an interrupted or reduced blood supply to the brain due to blood vessels blocked by fatty deposits (Andersen *et al.*, 2009; Jørgensen *et al.*, 1995). Hemorrhagic stroke occurs when there is a leakage or rupture of a blood vessel in the brain (Andersen *et al.*, 2009; Jørgensen *et al.*, 1995). There are multiple possible causes of hemorrhagic stroke including high blood pressure, anticoagulants, aneurysms, trauma, and cerebral amyloid angiopathy (Andersen *et al.*, 2009; Jørgensen *et al.*, 1995). Nevertheless, both types of stroke lead to cell death, which can cause a variety of disabilities in stroke survivors depending on the stroke location (Macciocchi *et al.*, 1998). When a stroke affects the motor cortex or projections originating from it, one can usually observe severe upper limb weakness and dysfunction, leading to a significant decrease in their quality of life (Broeks *et al.*, 1999).

As it stands, current rehabilitation protocols do not maximize stroke survivors' potential for recovery because brain plasticity and learning processes are not fully understood (DeJong *et al.*, 2005). It is thus crucial to better understand the brain mechanisms of movement production and find alternative rehabilitation techniques to maximize survivors' motor recovery.

1.2.3 Brain anatomy in the context of movement

The primary motor cortex (M1) is located along the precentral gyrus in the frontal lobe. It represents one of the most important brain areas associated with voluntary movement production (Lefebvre & Liew, 2017). M1 contains large pyramidal neurons with direct and indirect projections towards neurons in the spinal cord responsible for muscle contraction (Lemon *et al.*, 2008). The

tract through which the axons of these neurons travel is called the corticospinal (CS) tract, and these neurons are also known as CS neurons.

Due to the steep decline in brain volume observed within M1 and somatosensory areas, as well as increased axonal demyelination (Taubert *et al*., 2020), CS neurons are significantly affected and motor information passing through these neurons is delayed or disrupted. Consequently, a significant decline in motor hand movements is observed in the aging population (Smith *et al.*, 1999).

Since the CS tract crosses the body's midline, the M1 from each hemisphere controls the opposite side of the body (Lefebvre & Liew, 2017; Lemon *et al.*, 2008). In healthy individuals, each hemisphere sends reciprocal inhibitory signals to each other in order to provide good coordination between the two sides of the body (Nowak *et al.*, 2009). However, in stroke, the lesional hemisphere is weakened and cannot provide the same level of inhibition to the healthy hemisphere (Nowak *et al.*, 2009; Schlaug *et al.*, 2008). Thus, an imbalance in the interhemispheric inhibition is created where the affected side is largely restrained, a phenomenon causing greater motor dysfunction. Consequently, various rehabilitation protocols target these CS neurons in order to restore this interhemispheric imbalance and thus improve motor function in post-stroke individuals (Nowak *et al.*, 2009; Schlaug *et al.*, 2008).

Aside from M1, other brain areas are very important in motor control. For example, the dorsal premotor cortex which is part of premotor regions is associated with movement selection, the supplementary motor area (SMA) is located medial to the premotor cortex and is important in movement control and sequential motor learning, and the cerebellum is involved in movement control and coordination (Lefebvre & Liew, 2017). This study focuses primarily on M1 within the

sensorimotor cortices because of the presence of CS neurons providing direct and indirect projections toward the spinal cord (Lefebvre & Liew, 2017; Lemon *et al.*, 2008).

1.2.4 Brain oscillations & electroencephalography

Brain oscillations, also known as brain waves, are patterns of rhythmical or repetitive neuronal activity in the central nervous system (CNS). These oscillatory patterns are produced by individual neurons or neuronal interactions (Collura, 1993). Since individual neuronal recordings require invasive procedures as their electric potentials are too small to be captured from the surface of the head, most electrophysiological recordings performed in humans are done non-invasively and reflect the activity of populations of neurons (Nunez, 1981). At the population level, the synchronized activity of thousands or millions of neurons having a similar spatial orientation produces macroscopic oscillations which can be recorded from the surface of the head (Nunez, 1981). An example of such a non-invasive technique is EEG, which can measure the electric potential variations between different brain areas through electrodes placed on the scalp (Binnie & Prior, 1994). Thus, the cerebral activation detected by these electrodes reflects the neuronal activity of pyramidal cells situated near the surface of the scalp (Binnie & Prior, 1994).

Since EEG directly records the electric activity of neurons, it is one of the only non-invasive brain recording technologies capable of capturing the fast dynamic changes of neurons in the 10 to 100-millisecond range (Nunez & Srinivasan, 2007). However, the spatial resolution of EEG is lower compared to other brain imaging technologies such as computer tomography (CT), positron emitted tomography (PET), and [functional] magnetic resonance imaging ([f]MRI) (Nunez & Srinivasan, 2007). This low spatial resolution in EEG occurs due to excessive averaging of signals from thousands or millions of neurons located over a somewhat large region of the brain,

as well as due to volume conduction which occurs because of the blurring caused by the propagation of electrical fields through brain tissue and the skull (Nunez & Srinivasan, 2007). However, since these techniques do not directly capture the neuronal electrical activity, their temporal resolution is far inferior to EEG, making them inadequate for recording the oscillatory patterns in the brain (Dawson & Lauterbur, 2008; Nunez & Srinivasan, 2007).

1.2.5 Brainwave characteristics

As mentioned above, EEG recordings consist of the electrical activity averaged across thousands or millions of cortical neurons originating from a specific region of the brain (Nunez & Srinivasan, 2007). However, this raw signal is generally hard to interpret as is, which is why the different characteristics that this signal is composed of are investigated. The most important EEG parameters studied are the frequency and amplitude of a signal (Hu & Zhang, 2019).

The frequency of a brainwave represents the time scale at which an oscillation is completed, and it is measured in the number of cycles per second or Hertz (Hz) (Antal & Herrmann, 2016; Hu & Zhang, 2019). After numerous studies in which the brain was recorded at rest and during cognitive, perceptual, and sensorimotor activities, brain oscillatory activity was divided into five main frequency bands, namely: delta (< 4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (30-90 Hz) (Abhang et al., 2016; Başar et al., 2001; Buzsáki, 2006; Hu & Zhang, 2019). Each frequency band has been associated with specific brain states. For example, delta waves are linked with sleep, theta waves are associated with an inward focus, alpha and beta waves are related to attention, and gamma waves are linked with concentration (Abhang et al., 2016; Başar et al., 2001; Buzsáki, 2006; Hu & Zhang, 2019).

However, the raw EEG signal recorded from electrodes never oscillates at a single frequency or within a single frequency band (Hu & Zhang, 2019). Instead, the signal oscillates to a certain degree over the entire frequency spectrum from ~0.5Hz to ~80Hz (Hu & Zhang, 2019). To quantify the amount of signal present at a given frequency or within a given frequency band, a technique termed time-frequency analysis is often used (Hu & Zhang, 2019; Tadel *et al.*, 2019). This method extracts the power of a signal in the time domain (i.e. time series) at each frequency and time point of interest (Hu & Zhang, 2019; Tadel *et al.*, 2019), thus determining which frequencies are predominant at a given time for a given electrode.

The amplitude of an oscillatory signal represents the strength of the neuronal electrical activity and is usually measured either in terms of potential difference in microvolts (μV) or picovolts (pV), or in terms of power in $\mu V^2/Hz$ or pV^2/Hz (Hu & Zhang, 2019). Changes in amplitude reflect fluctuations in the amount of synchronization of oscillatory activity between different populations of neurons such that the higher the amplitude, the greater the synchronization (Pfurtscheller & Lopes da Silva, 1999). Synchronization occurs when populations of neurons oscillate at the same frequency and their position in the oscillation (i.e., their phase) also matches (Fries, 2015; Varela et al., 2001). Conversely, desynchronization is the process through which already synchronized neuronal populations change their oscillatory frequency and/or their phase of oscillation (Varela et al., 2001).

1.2.5.1 Movement-related beta oscillations

Beta activity is found across multiple regions of the brain and is associated with many brain states such as anxiety, external attention, and relaxation (Abhang *et al.*, 2016; Spitzer & Haegens, 2017). In particular, its presence within the sensorimotor areas along with its relation to voluntary

movement activity has been a great focus of many researchers (Cheyne, 2013; Spitzer & Haegens, 2017). Within this brain region, beta activity has been correlated with voluntary movement, and more specifically, detecting intention of movement, motor learning, and motor performance (Cheyne, 2013).

Movement-related beta oscillations are patterns of brain activity in the beta frequency band observed in response to movement. These oscillatory patterns involve a relatively high baseline beta power before movement initiation, reflecting the resting beta-band activity, which is followed by a suppression during voluntary movement termed MRBD. The transient increase in beta power after movement termination is known as post-movement beta rebound (PMBR) (Pfurtscheller & Lopes da Silva, 1999; Stancák Jr & Pfurtscheller, 1995). Since each EEG electrode reflects the ongoing processes of thousands or tens of thousands of neurons, it is generally hard to observe these patterns in each trial due to a large amount of noise in the signal. Thus, it is important to conduct multiple trials and average the brain activity across all of them such that random noise is averaged out and relevant patterns become evident (Coles & Rugg, 1995; Pfurtscheller & Lopes da Silva, 1999).

The modulations in the beta band are thought to reflect changes in synchrony between neurons located in the sensorimotor cortex that is regulated by a complex balance between inhibitory GABAergic neurons and excitatory glutamatergic neurons (Pfurtscheller & Lopes da Silva, 1999; Premoli *et al.*, 2017; Stancák Jr & Pfurtscheller, 1995). A highly synchronized beta activity corresponds to a deactivated state of the motor cortex and a decreased cellular excitability in thalamocortical systems (Pfurtscheller & Lopes da Silva, 1999). In contrast, beta desynchronization relates to the activation of cortical areas responsible for movement production (Pfurtscheller & Lopes da Silva, 1999). It can be thus theorized that a lower resting-state beta

activity and a higher MRBD during a motor task would reflect increased activation in the motor cortex and be correlated with enhanced motor performance due to increased ease in executing the movement. This theory seems to be supported in the literature for patient populations who present motor deficits. In fact, elderly and Parkinson's individuals show abnormally higher resting baseline beta activity compared to healthy controls (Brown, 2007; Heinrichs-Graham & Wilson, 2016). Interestingly, elderly subjects have higher MRBD compared to younger controls and a higher MRBD is associated with worse motor performance in these subjects (**Figure 1**) (Xifra-Porxas *et al.*, 2019). However, even though their MRBD is higher, the absolute beta power during movement is still higher in elderly participants compared to younger individuals due to their higher overall resting beta state (Heinrichs-Graham & Wilson, 2016). This suggests that the higher MRBD observed in elderly subjects may be due to the brain trying to overcompensate for the desynchronization in the beta band to decrease the absolute beta activity low enough for movement production to be accomplished. This attempt is only partially successful since elderly subjects still show higher beta power during movement and also show worse motor performance compared to younger controls (Heinrichs-Graham & Wilson, 2016; Rossiter *et al.*, 2014). Consequently, the above-mentioned theory is still supported in elderly subjects.

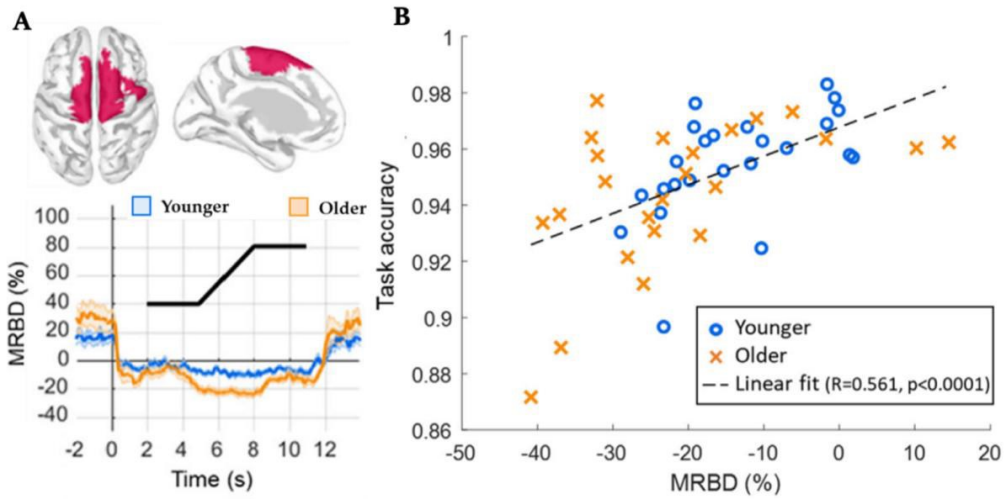

Figure 1. *A: MRBD pattern in older and younger adults in M1 during a motor handgrip task; B: Correlation between MRBD values and task accuracy in older and younger adults (Xifra-Porxas et al., 2019).*

Several studies have looked at movement-related beta oscillations in the context of stroke. Studies have found a decreased absolute beta activity during rest and various motor tasks in the affected hemisphere compared to the unaffected one and compared to control subjects (Kulasingham *et al.*, 2021; Rossiter *et al.*, 2014). It has also been reported that stroke individuals show lower MRBD during movement of the hand in the affected sensorimotor cortex compared to the unaffected hemisphere and healthy individuals. Higher beta power and lower MRBD are associated with worse motor performance in these participants (Kulasingham *et al.*, 2021; Rossiter *et al.*, 2014; Shiner *et al.*, 2015; Thibaut *et al.*, 2017). This aligns well with the theory that motor activity is enhanced when the sensorimotor cortex is highly activated, a phenomenon occurring when this region exhibits low beta power.

Finally, the transient increase in beta power above baseline observed after movement termination known as PMBR can last up to 9 seconds before returning to baseline (Pakenham *et al.*, 2020; Pfurtscheller & Lopes da Silva, 1999). PMBR reflects an over-synchronization of neurons and is associated with a considerably reduced excitability of motor cortex neurons (Chen

et al., 1998; Pfurtscheller & Lopes da Silva, 1999). Higher PMBR during a visuomotor learning task has been associated with improved motor performance (Espenhahn *et al.*, 2019). However, more interestingly, PMBR is also related to motor skill learning such that higher PMBR predicts better learning and thus better performance in the task when performed 24 hours after the training (Espenhahn *et al.*, 2020).

1.2.5.2 Beta bursts

For many years, it has been unclear what are the exact mechanisms through which oscillatory activity is generated in the brain. A common assumption is that brain waves are caused by the dynamic synchronization and desynchronization of groups of neurons firing at a particular frequency, resulting in sustained oscillatory activity (Buzsáki, 2010). However, this view has been recently challenged as it has been argued that high amplitude transient bursts of activity in the beta frequency range are at the origin of oscillatory patterns and the observed sustained activity in patterns like the MRBD is the consequence of averaging across multiple trials (**Figure 2)** (Feingold *et al.*, 2015; Jones, 2016; Little *et al.*, 2019; Shin *et al.*, 2017). In fact, it has been suggested that these bursts emerge from an alternating dipole current originating from the supragranular and infragranular layers targeting dendrites of pyramidal neurons in almost synchronous bursts of excitatory synaptic activity (Sherman *et al*., 2016).

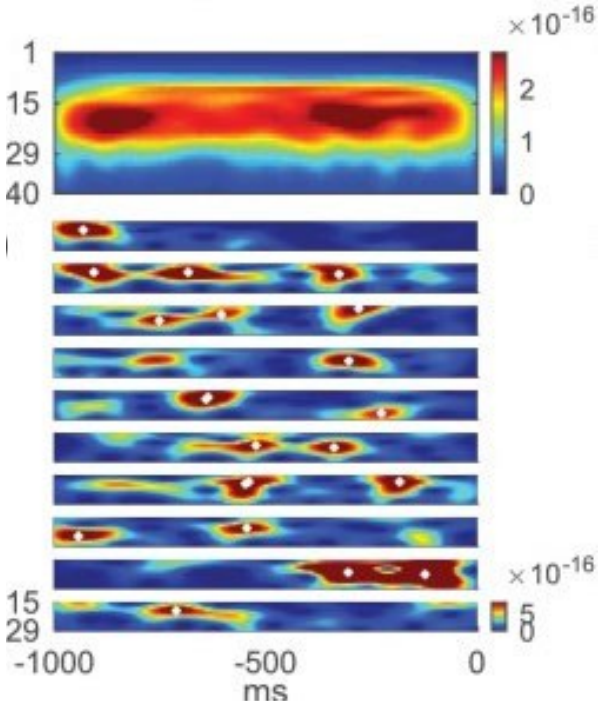

Figure 2. *Beta bursts detected in individual trials resulting in a seemingly sustained beta activity when signals are averaged across trials (Shin et al., 2017).*

Several characteristics can be extracted from these beta bursts, with the primary ones being the rate (number of bursts detected per second), amplitude (maximum power reached within a burst), and duration (duration over which a burst is above a specified threshold) (Shin *et al.*, 2017; Yu *et al.*, 2021). It has been assumed that these burst characteristics can directly influence the averaged beta activity such that a higher rate, a higher amplitude, and a higher duration contribute to a higher beta power activity (**Figure 3**) (Shin *et al.*, 2017).

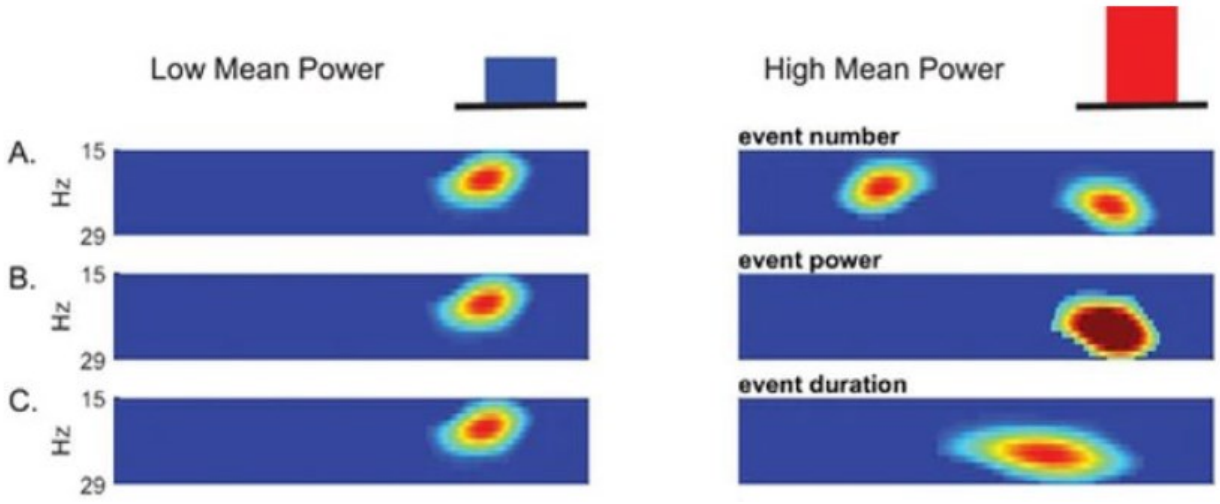

Figure 3. *Visualization of beta burst characteristics (event number, power, duration), and the way these characteristics are association with a lower or a higher mean beta power (Shin et al., 2017).*

In healthy participants, a lower burst rate and burst amplitude before movement initiation has been associated with shorter reaction time in a button-pressing task (Little *et al*., 2019). Importantly, if the burst rate or burst amplitude is lower, the overall beta activity when averaging the data across trials will also be reduced. Thus, these observations agree with the argument that a lower beta-band resting state and higher MRBD would predict enhanced motor performance. A magnetoencephalography (MEG) study observed an association between burst characteristics and age when looking at individuals between 18 and 88 years old in the context of a finger-tapping task (Brady *et al.*, 2020). Both burst rate and amplitude are associated with age, but only the burst rate showed a clear linear trend with age, while burst amplitude showed a quadratic trend. Older individuals were found to have a higher pre-movement burst rate and a lower post-movement burst rate, but no differences were found for the movement phase (Brady *et al.*, 2020). Another recent MEG study looked at the MRBD and beta bursts in older and younger individuals while they performed a handgrip task with their right hand (Chatterjee, 2022). The results showed that older

subjects have a higher burst amplitude than younger participants across all movement phases and during the resting-state period. No differences were observed for rate and duration. Moreover, burst amplitude during the movement phase was shown to be lower than both the pre-movement and the post-movement phases, a pattern consistent with the MRBD pattern. Burst rate was only shown to be lower than the post-movement phase and burst duration did not significantly change across the movement intervals (Chatterjee, 2022). Although these results are not completely consistent with those from Brady *et al.* (2020), both studies show that potentially both rate and amplitude are related to aging. To our knowledge, no studies on beta bursts have been formally investigated in stroke survivors.

1.2.6 Non-invasive brain stimulation (NIBS) techniques

As the name suggests, NIBS involves techniques capable of modulating brain activity from the surface of the scalp without requiring any incisions or other invasive methods. One of the most common types of NIBS that has been increasingly used in research in recent years is transcranial electrical stimulation (tES) (Polanía *et al.*, 2018). tES involves electrodes placed on the surface of the scalp through which electrical current is passed at low intensity (1–2 mA). A certain amount of current can travel across the skull such that it modifies the neuronal activity by changing the action potential threshold of neurons to either facilitate or inhibit the probability of a neuronal discharge occurring (Nitsche & Paulus, 2000; Polanía *et al.*, 2018). Conventionally, the current is passed through two relatively large electrodes (~25 cm^2), one being placed over the brain region of interest (ROI) being studied while the other one is usually placed in an area unrelated to the cerebral processes studied such as the forehead (Nitsche & Paulus, 2000; Woods *et al.*, 2016). Such an approach provides a relatively widespread stimulation of brain regions. For a more targeted stimulation approach, a more recent technique called HD-tES can be used (**Figure 4**) (Wu

et al., 2021). This method involves 5 small ring electrodes (~0.5 cm^2) placed such that one of them (the active electrode) is positioned right above the ROI while the other 4 are placed about 3 cm around it (Datta *et al.*, 2009). In this setup, current travels from the active electrode towards the other 4 or vice-versa.

Depending on the type of current used, the most common tES techniques are transcranial direct current stimulation (tDCS) and tACS.

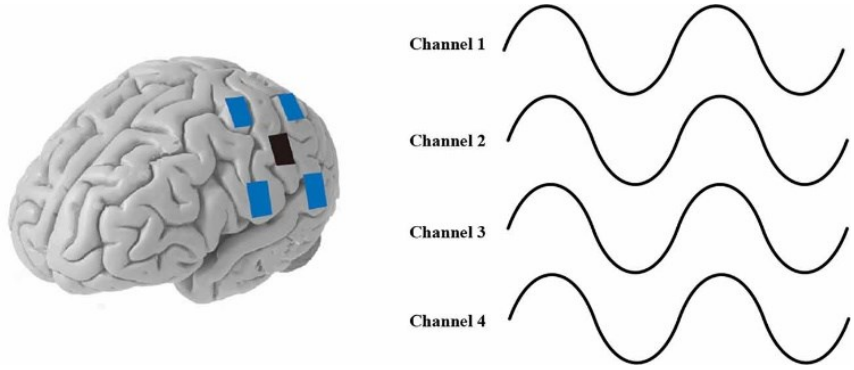

Figure 4. *Visualization of the setup for HD-tES consisting of 5 small ring electrodes placed on the scalp. The active electrode is shown in black (Wu et al., 2021).*

1.2.6.1 Transcranial direct current stimulation (tDCS)

tDCS is the first tES technique invented and it involves the application of a weak direct electrical current (1–2 mA) through the scalp (Woods *et al.*, 2016). The current is passed from one or more electrodes called the anode(s) to one or more electrodes called the cathode(s). If the anode is placed right above the ROI, it is considered an anodal stimulation, while if the cathode is the one placed over the ROI, the stimulation is considered cathodal (Woods *et al.*, 2016).

Different stimulation setups can have different effects on the brain. Generally, anodal stimulation has been shown to increase the excitability of motor cortex neurons for several minutes after stimulation, while cathodal stimulation seems to have the opposite effect (Nitsche & Paulus,

2000). Compared to sham and cathodal stimulation, anodal stimulation has also been shown to promote motor skill acquisition and exhibit greater long-term retention when participants were tested 3 months later (Reis *et al.*, 2009). The duration and intensity of the stimulation also seem to play an important role. A stimulation duration below 5 min has been shown to not be able to provoke considerable after-effects, while extending the stimulation over 20 min or 2 mA may not necessarily induce an increase in the stimulation effects and, on the contrary, it might actually invert these effects (Batsikadze *et al.*, 2013; Nitsche & Paulus, 2000; Woods *et al.*, 2016).

Both anodal and cathodal stimulation have been used in stroke survivors, but not all studies show congruent results. Some studies reported that both anodal and cathodal stimulation show long-lasting improvement in motor performance, while others do not observe any changes or only report improvement in some participants (Hesse *et al.*, 2007; Nair *et al.*, 2008; Solomons & Shanmugasundaram, 2019).

1.2.6.2 Transcranial alternating current stimulation (tACS)

tACS is a more recent tES technique that resembles tDCS except that a weak sinusoidal electrical current is passed through the scalp instead (Solomons & Shanmugasundaram, 2019; Woods *et al.*, 2016). Although the basic electrode montage is similar between tDCS and tACS, there is no notion of anodal or cathodal electrodes for tACS since current is passed in both directions in a cycle. On average, the membrane potential of neurons remains unchanged as the cells get equally excited and inhibited during a cycle (Woods *et al.*, 2016). Thus, the main objective of tACS is not to modify the excitability of a brain region. Instead, tACS entrains brain oscillations at specific rhythms (Herrmann *et al.*, 2013).

Similar to tDCS, the most common tACS parameters involve an amplitude between 0.4 mA to 2 mA and duration between 5 min to 20 min (Takeuchi & Izumi, 2021). Aside from the

amplitude and duration of the stimulation, another important parameter for tACS is the oscillation frequency dictating how long the sinusoidal cycles are. Different oscillatory frequencies seem to have a strong impact on motor performance and supposedly have a different impact on various brain oscillatory rhythms. For instance, it has been shown that cortical stimulation at 70 Hz can speed the voluntary force generation in a go/no-go task, while stimulation at 20 Hz slows the voluntary force generation in the same task (Joundi *et al.*, 2012). In another study, 20 Hz tACS was shown to slow voluntary movement in a motor task where participants control a joystick with their dominant hand (Pogosyan *et al.*, 2009). However, many studies show mixed results regarding the effects of alpha tACS (10 Hz) and beta tACS (20 Hz) over M1. In some cases, it was shown that both alpha tACS and beta tACS can enhance motor skill acquisition before and during training, while in others, it was observed that alpha tACS and beta tACS either have no effect or may even impair motor skill acquisition (Lafleur *et al.*, 2021; Takeuchi & Izumi, 2021). Moreover, both alpha tACS and beta tACS seem to have either a detrimental effect or no effect at all on motor skill consolidation after learning (Takeuchi & Izumi, 2021). Although fewer studies have been performed using high-gamma tACS (70 Hz) over M1, the findings seem to be much more consistent. Most of these studies show that corticospinal excitability is increased and motor skill acquisition is improved when high-gamma stimulation is applied before and during training (Joundi *et al.*, 2012; Solomons & Shanmugasundaram, 2019; Takeuchi & Izumi, 2021). Examples of such motor enhancements include an increase in hand and finger movement velocity and force (Takeuchi & Izumi, 2021). Nevertheless, some studies show that high-gamma tACS may have a negative effect on motor skill retention when participants are retested at a later date (Takeuchi & Izumi, 2021).

A recent study performed on elderly individuals performing a unimanual motor handgrip task showed that 20 Hz tACS causes an increase in MRBD 15 minutes post-stimulation, while 70 Hz tACS causes a decrease in MRBD 15 minutes post-stimulation (Morales Fajardo, 2023). However, no studies to our knowledge looked at the effects of tACS stimulation on beta bursts in older subjects.

Few tACS studies have been performed in the context of stroke, and no tACS study up-to-date has shown improvement in motor recovery after stroke by modulating brain rhythms (Takeuchi & Izumi, 2021). Beta tACS over the ipsilesional M1 was able to improve the classification accuracy of a brain-computer interface during motor imagery in stroke participants by significantly reducing the variance in the resting beta activity (Naros & Gharabaghi, 2017). However, the resting beta power or the MRBD power was unaffected in the above study (Naros & Gharabaghi, 2017).

1.3 Rationale

Movement-related beta oscillations recorded with EEG in the context of movement of the hand have been studied in depth across the years (Pfurtscheller & Lopes da Silva, 1999; Stancák Jr & Pfurtscheller, 1995). Similarly, NIBS techniques such as tDCS and tACS have also become increasingly popular (Takeuchi & Izumi, 2021; Woods *et al.*, 2016). However, few studies have combined these technologies, especially in the context of aging and stroke. Moreover, beta bursts have recently gained popularity and might be at the origin of sustained beta oscillatory activity (Feingold *et al.*, 2015; Jones, 2016; Little *et al.*, 2019; Sherman *et al.*, 2016; Shin *et al.*, 2017). However, the relation between beta burst characteristics and averaged beta power is still unclear and no studies have looked at the effects of NIBS on beta bursts in aging and stroke.

1.4 Objectives

The objectives of this study are the following:

- Determine the link between beta bursts and previously described beta power analysis on the same subjects.
- Quantify the effect of 20Hz & 70Hz HD-tACS on beta bursts in elderly individuals.
- Assess how long these effects persist after the stimulation.
- Compare beta burst characteristics and beta power between elderly and stroke subjects.

1.5 Hypotheses

Based on the results from Chatterjee (2022) and Brady *et al.* (2020), it is hypothesized that both burst rate and burst amplitude are closely related to beta power and follow an MRBD-like pattern, meaning that the rate and amplitude during the movement interval is lower compared to the pre-movement and post-movement intervals.

The elderly dataset used for this study was obtained from Morales Fajardo (2023) and the analysis performed in that study focused on the effects of 20 Hz & 70 Hz HD-tACS on resting-state beta power and MBRD. The results obtained showed that 20 Hz tACS caused an increased MRBD (meaning a more negative MRBD) 15 minutes post-stimulation, and 70 Hz tACS caused a decreased MRBD (meaning a less negative MRBD) 15 minutes post-stimulation (Morales Fajardo, 2023). Given that it is expected that both burst rate and burst amplitude are closely related to MRBD values, it was hypothesized that 20 Hz tACS stimulation would cause a decrease in burst rate and amplitude, while 70 Hz tACS stimulation would cause an increase in burst rate and amplitude. No significant changes were expected for burst duration.

Finally, the stroke dataset used in this study is incomplete and thus no robust statistical analyses will be used to compare the elderly and stroke subjects. Nevertheless, it was hypothesized that

elderly individuals would show a higher beta power, a higher burst rate, and a higher burst amplitude compared to stroke participants given that older individuals are known to have a higher overall beta power compared to younger individuals (Xifra-Porxas *et al.*, 2019), while stroke survivors show a lower beta power in the affected hemisphere compared to controls (Kulasingham *et al.*, 2021; Rossiter *et al.*, 2014).

CHAPTER 2: METHODOLOGY

This study used a previously collected dataset in which EEG data was recorded in older individuals at rest and during a handgrip motor task under the effects of 20 Hz, 70 Hz, and sham HD-tACS protocols (Morales Fajardo, 2023). Another initial dataset involving stroke participants was also used for exploratory analysis. Both experiments were conducted at McConnell Engineering Building at McGill University and received ethical approval.

2.1 Elderly dataset

As mentioned above, the following dataset was obtained from a study conducted by Morales Fajardo (2023) and approval to use the data was granted for the current study.

2.1.1 Study Participants

15 healthy older individuals (7 males, 8 females) were recruited in this study. Previous studies applying tDCS or tACS as a neuro-modulatory stimulus have shown changes in brain networks and behaviour using this sample size or less (Tavakoli & Yun, 2017; Wach *et al.*, 2013). The inclusion and exclusion criteria were the following:

Inclusion criteria:

- Healthy male or female over 65 years old
- Right-handed [assessed through The Edinburgh Handedness Inventory (Oldfield, 1971)]

Exclusion criteria:

- Have any medically diagnosed condition or history of neurological or psychiatric disorder
- Have any contraindications to non-invasive brain stimulation [assessed through the NIBS safety questionnaire]
- Have received tDCS or tACS stimulation in the last three months
- Have cognitive impairments [assessed by having the Mini-Cog Test result < 3 (Borson et al., 2000)]

2.1.2 Experimental Paradigm

Figure 5 summarizes the experimental paradigm in this study. Participants visited the laboratory on 4 occasions. The first session was an eligibility session, while the three subsequent sessions were the experimental sessions, which were conducted one week apart from each other.

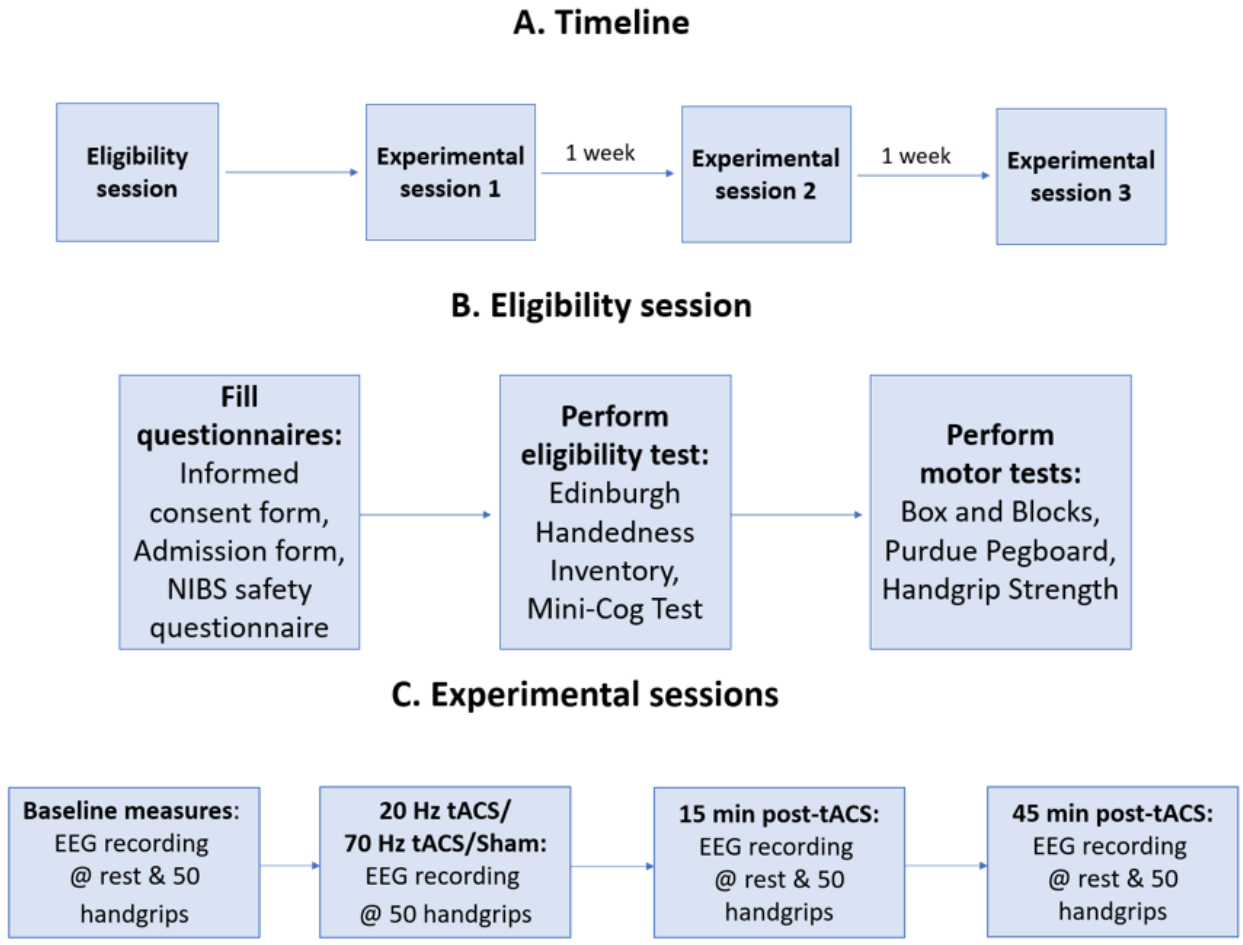

Figure 5. *Experimental paradigm for the elderly study. (A) Participants visited the laboratory on 4 occasions over 3 weeks. Participants first came for the eligibility session (B) in which they fill*ed *the admission questionnaires and performed the eligibility and motor tests. Then, participants came for three experimental sessions (C) taking place 1 week apart. In these sessions, EEG was recorded while the participant was at rest and while performing 50 trials of a motor handgrip task. Next, 20 Hz tACS, 70 Hz tACS, or sham stimulation is applied while the participant performs the motor task. Finally, the resting state and motor task were repeated 15 minutes and 45 minutes post-tACS.*

2.1.2.1 Eligibility session

During the first visit (**Figure 5-B)**, participants filled out the informed consent form and completed the admission form to collect data regarding their socio-demographic characteristics (e.g., age, gender, maternal language, handedness, occupation, hobbies). Next, the eligibility of the participants was tested by completing the NIBS safety questionnaire (ensuring no contraindications related to tACS) (Brunoni *et al.*, 2011), the Edinburgh Handedness Inventory (ensuring participants are right-handed) (Oldfield, 1971), and the Mini-Cog Test (ensuring no mental impairments) (Borson *et al.*, 2000).

Participants underwent motor assessment using the Box and Block Test (BBT) (Mathiowetz *et al.*, 1985A), Purdue Pegboard Test (PPT) (Lindstrom-Hazel, 2015), and Handgrip Strength Test (HGS) (Bohannon *et al.*, 2006) to characterize the sample studied.

- BBT: measures gross manual dexterity by moving as many boxes as possible from one compartment to another in 60 seconds.
- PPT: measures fine manual dexterity by placing as many pins as possible into the holes of a board in 30 seconds (left, right, both hands), and assembling as many pins, collars, and washers as possible in 60 seconds.
- HGS: measures the maximum voluntary contraction (MVC) by squeezing a dynamometer for 5 seconds as hard as possible three times with each hand.

2.1.2.1 Experimental sessions

The next 3 experimental sessions were separated by one week, each having the following paradigm (**Figure 5-C)**. Resting-state EEG was recorded for 5 minutes, and subjects were instructed to stare at a white cross displayed on a screen in front of them. Then, participants performed 50 trials of a handgrip task at 15% of their MVC with their right hand. The resting-state and motor paradigm are illustrated in **Figure 6** (Morales Fajardo, 2023). During the handgrip task,

a movable indicator was displayed for 4 seconds on the screen that raises as the gripper is squeezed and lowers as the gripper is released. Participants were instructed to exert force on the gripper in order to reach a red target bar (corresponding to 15% of their MVC) as fast and as accurately as possible and maintain the force until the trial ended. In between trials, a white cross was displayed on the screen for a random period of time between 8 and 10 seconds, where participants were instructed to release the gripper and stare at the cross until the next trial began. Following these baseline measures, participants received either 20 Hz HD-tACS, 70 Hz HD-tACS or sham stimulation randomized across the 3 visits while performing the above-mentioned handgrip task. EEG data was collected continuously while stimulation took place. Participants remained blinded to the type of stimulation received each time. After the stimulation ended, the same EEG data collected at baseline was repeated (rest & 50 repeats of handgrips) 15 and 45 minutes post-tACS/sham.

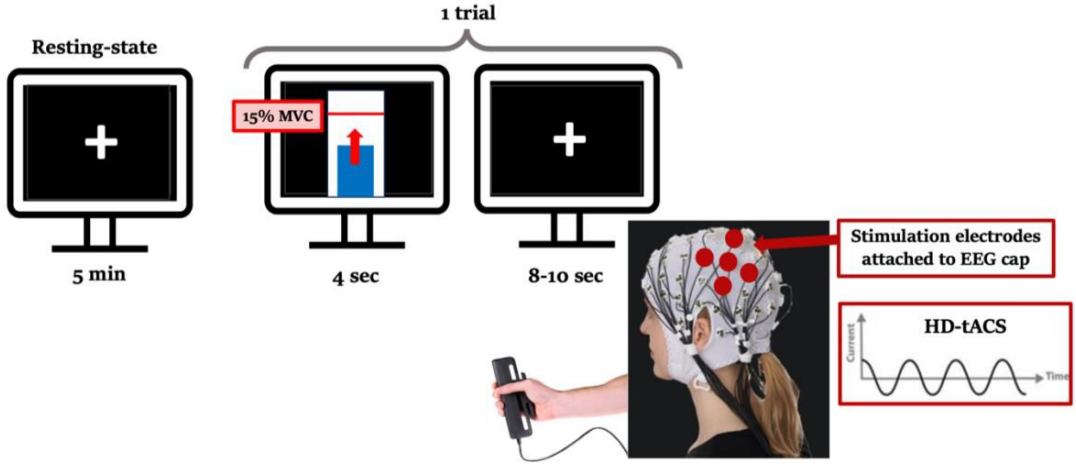

Figure 6. *Resting-state and motor paradigm (Morales Fajardo, 2023). The resting-state EEG recording is represented on the left where participants were asked to stare at the white cross in the middle of the screen for 5 minutes. One trial of the handgrip motor task is illustrated in the middle and consisted of a 4-second period during which the participant is asked to squeeze the gripper so that the blue bar reaches the red line, which was set to 15% MVC, followed by an inter-trial period of 8-10 seconds during which the participant is asked to release the gripper and prepare for the next trial. The stimulation electrodes delivering the brain stimulation are illustrated on the right and are situated over the left M1 (electrodes FC5, FC1, C3, CP5, CP1).*

2.1.3 Measurements and Study Instruments

Questionnaires: The admission form was used to collect information such as age, sex, occupation, leisure activities, and general health condition during the first session. The NIBS safety questionnaire was used to identify participants with a higher risk of adverse effects to NIBS in order to exclude them from the study. The Activity Log questionnaires (Day and Evening) were given on each experimental day to monitor the subjects' caffeine intake, activity level, and sleeping or napping. These features were assessed since they can potentially interfere with the subject's ability to learn the motor task. To record any possible adverse effects for tACS, a modified version of a post-NIBS questionnaire introduced by Brunoni *et al.* (2011) was used. The following side-effects were included: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating and acute mood change. Specifically, participants were asked to indicate the intensity of the side-effect (1, absent; 2, mild; 3, moderate; 4, severe) and if they attribute the side-effect to the stimulation (1, none; 2, remote; 3, possible; 4, probable; 5, definite) (Neuling *et al.*, 2013).

Electroencephalography (EEG): Participants had their head measurements taken to select the appropriate 64-channel EEG electrode net (Brain Products, Germany) for their head size. To determine the circumference of the participant's head, the nasion and the inion were used as landmarks. The center of the head (Cz, as determined using the 10-20 system (Homan *et al.*, 1987)) was marked with an erasable pen to center the EEG cap (Klem *et al.*, 1999). Once the cap was placed on the participant's head, the impedance of the electrodes was checked, and EEG gel was added to the electrodes accordingly such that the electrode impedances were kept below 20 kΩ. The signals were sampled at 2500 Hz. EEG data was collected during resting states and isometric grip contraction, including when tACS was applied, in order to monitor the online effects of each

type of stimulation on brain activity. EEG-based beta bursts were extracted from the data collected during the resting-state and handgrip task.

Transcranial alternating current stimulation (tACS): 20 Hz HD-tACS, 70 Hz HD-tACS or sham stimulation was applied during a block of 50 handgrips after the baseline measurements were taken on each experimental session. Stimulation was triggered by an EEG-compatible high-density electrical current generator for brain stimulation (Soterix Medical, Germany). HD-tACS was applied over the left M1 for 10 minutes (**Figure 7**). HD-tACS was applied at 20 Hz or 70 Hz with 1 mA peak-to-peak amplitude. Electrode placement in all cases was determined following the 10-20 EEG placement system (Homan *et al.*, 1987). The stimulation electrodes were filled with the gel provided by Soterix Medical to deliver current.

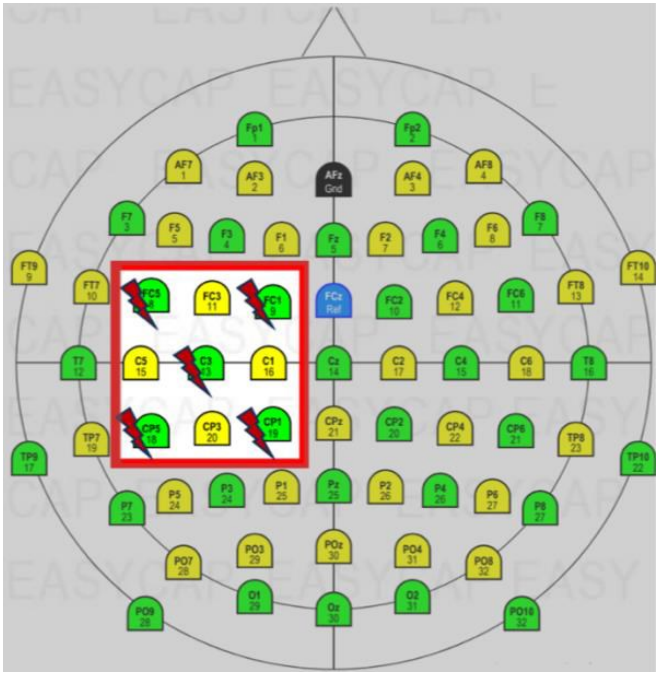

Figure 7. *EEG cap (Morales Fajardo, 2023). The stimulation electrodes delivering the brain stimulation are illustrated by a flash in the red rectangle and were situated over the left M1 (electrodes FC5, FC1, C3, CP5, CP1).*

Hand gripper: Participants used a hand gripper system (BIOPAC, USA) during the execution of the motor task using their right hand.

Maximal Voluntary Contraction (MVC): To conduct the isometric grip contraction task, the MVC of each participant was measured. Subjects followed instructions from a computer and squeezed the hand gripper with as much force as possible (Dal Maso *et al.*, 2018).

Isometric Grip Contraction task: Participants were sitting in front of a screen holding a hand gripper with their right hand. They were required to squeeze the gripper with 15% of their MVC. EEG data was collected during the process. The motor task consisted of 50 trials in total (Xifra-Porxas *et al.*, 2019).

2.2 Stroke dataset

The stroke dataset used in this study is incomplete as the recruitment is still ongoing. The post-COVID-19 circumstances made the participants' recruitment difficult to complete before the writing of this thesis. Consequently, this dataset is only used for exploratory purposes, and no robust statistical analyses have been performed on it.

2.2.1 Study participants

In this study, 3 subjects were recruited (2 males, 1 female) out of 15 subjects that will participate in total. The inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Male or female who had a stroke more than 6 months prior to the first visit to the lab

Exclusion criteria:

- Have any contraindications to tDCS/tACS stimulation [assessed through the NIBS safety questionnaire]
- Have received tDCS or tACS stimulation in the last three months

- Have cognitive impairments [assessed by having the Mini-Cog Test result < 3 (Borson *et al.*, 2000)]
- Have severe hemineglect (>70% on the Line Bisection Test (Agrell *et al*., 1997))
- Have severe spasticity (≥ 3 on the Modified Ashworth Scale (Brashear *et al*., 2002))

2.2.2 Experimental Paradigm

The experimental paradigm in this study is very similar to the one in the elderly study (see section **2.1.2**), but there are some key differences that will be explained below. **Figure 8** summarizes the experimental paradigm for the stroke study.

In the eligibility session, the admission form also required participants to provide information about their stroke, such as the location in the brain of the stroke, date of the stroke, which hand is most affected by the stroke, etc. There were also some differences in the eligibility tests performed. In contrast to the elderly study, the Edinburgh Handedness Inventory (Oldfield, 1971) was not performed on stroke participants. Instead, other eligibility tests were performed, such as the Line Bisection Test (Agrell *et al*., 1997) and the Modified Ashworth Scale (Brashear *et al*., 2002). The Line Bisection Test was used to detect whether participants showed signs of hemineglect by placing in front of them a piece of paper containing small lines spread across it and asking the subjects to cross all the lines they saw. The Modified Ashworth Scale was used as a clinical spasticity assessment in which different muscle groups (shoulder, elbow, wrist, fingers, thumb) are rated from 0 to 4, depending on how much spasticity they present. Finally, for the motor tests, PPT was not performed on stroke participants. Instead, the Nine Hole Peg Test (9HPT) (Mathiowetz *et al.*, 1985B) and the Fugl-Meyer Upper Limb Assessment (FMA-UL) (Sanford *et al*., 1993) were conducted instead. The 9HPT was used to assess the finger dexterity of subjects by placing nine pins in holes on a board and removing them afterwards as fast as possible. The

FMA-UL was used on stroke survivors to determine the amount of disability present in the affected limb compared to the unaffected limb with a score out of 66 points.

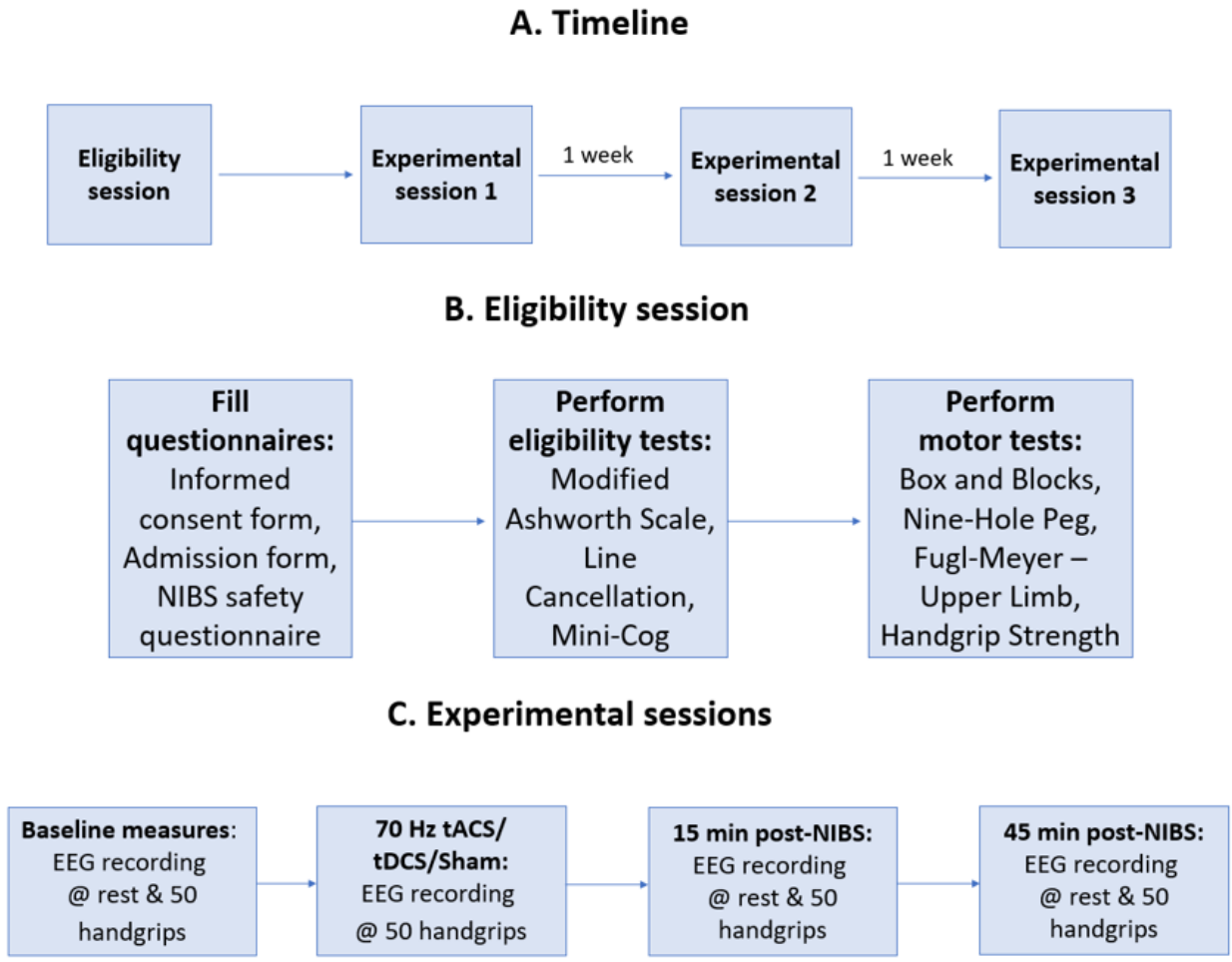

Figure 8. *Experimental paradigm for the stroke study. (A) Participants visited the laboratory on 4 occasions over 3 weeks. Participants first came for the eligibility session (B) in which they fill the admission questionnaires and performed the eligibility and motor tests. Then, participants came for three experimental sessions (C) taking place 1 week apart. In these sessions, EEG was recorded while the participant was at rest and while performing 50 trials of a motor handgrip task. Next, 70 Hz tACS, anodal tDCS, or sham stimulation was applied while the participant performed the motor task. Finally, the resting state and motor task were repeated 15 minutes and 45 minutes post-NIBS.*

The experimental sessions in the stroke study were almost identical to the ones in the elderly study. One difference is that the stimulation protocols used for each session were different. While the elderly study used 20 Hz tACS, 70 Hz tACS, and sham stimulation protocols, the stroke study used 70 Hz tACS, anodal tDCS, and sham stimulation protocols. The anodal HD-tDCS was applied at 2 mA. Another difference from the elderly study was that participants performed the motor task using their affected hand (left or right) instead of always using their right hand. Moreover, the HD-tDCS and HD-tACS were applied over the M1 contralateral to the moving hand. Thus, if the right hand was affected, then stimulation was applied over the left M1 (electrodes FC5, FC1, C3, CP5, CP1), while if the left hand was affected, then stimulation was applied over the right M1 (electrodes FC6, FC2, C4, CP6, CP2).

2.3 Data analysis

2.3.1 Data preprocessing

The EEG data was preprocessed using the *Brainstorm* MATLAB toolbox (Tadel *et al*., 2011). The power spectrum density was first calculated to detect and remove atypical electrodes through visual inspection. Then, the EEG data was band-passed between 0.5 Hz and 100 Hz, and a notch filter was used at 60 Hz to remove powerline artifacts. The data was then resampled at 250 Hz and re-referenced to an average reference. Afterwards, noisy segments (e.g., caused by the movement of the participant) were removed by visual inspection. Next, other artifacts (muscle, eye blink, saccades, heart) were identified and removed using Independent Component Analysis (ICA). This part of the preprocessing was already done by Morales Fajardo (2023) when the dataset was acquired.

After the raw data had been preprocessed, the data were separated into epochs differently for the resting state blocks and the motor blocks. The resting state blocks were separated into 3s segments, while the motor blocks were epoched from 1.5s before the beginning of each trial to 10.5s after trial initiation. Time 0s is the moment when the blue bar appeared and the subjects were required to squeeze the gripper. From each time block, the first 5 trials were removed, as well as any other trials containing noisy segments identified through visual inspection. Next, each trial from the motor blocks was further separated into 3 segments. The pre-movement phase used the EEG signal between 1.1s and 0.1s before trial initiation, the movement phase used the EEG signal between 0.5s and 3.5s after trial initiation, and the post-movement phase used the EEG signal between 5s and 8s after trial initiation. Finally, all the resting state and motor epochs were exported from MATLAB for beta burst extraction (see section **2.3.2**).

2.3.2 Beta burst extraction

All the signals further analysed were extracted from the C3 electrode (located over the left sensorimotor areas) for subjects performing the motor task with the right hand (all elderly participants and 2 stroke participants) or from the C4 electrode (located over the right sensorimotor areas) for subjects performing the motor task with the left hand (1 stroke participant).

Beta burst extraction was performed using the same methodology as Tinkhauser *et al.* (2017a). Single-trial EEG waveforms were extracted from each time block and decomposed into the time-frequency (TF) domain and band passed in the beta frequency range (15-29 Hz). Next, the amplitude envelope was extracted. For each interval of interest (rest, pre-movement, movement, post-movement) in every epoch, a threshold corresponding to the 75^{th} percentile of the absolute beta power within that segment was calculated. Bursts were detected when the signal

surpassed this threshold for a minimum duration of 100ms to exclude rapid fluctuations that may result in false bursts.

For each beta burst detected, the following characteristics were extracted:

- Burst rate: Number of bursts per second (events/sec)
- Burst amplitude: Maximum amplitude power reached within a burst (pV)
- Burst duration: Duration over which the burst is above the specified threshold (ms)

After some preliminary results, it was observed that bursts extracted from shorter intervals are underestimated compared to bursts extracted from longer ones, meaning that the burst rate extracted from shorter intervals is lower than the burst rate extracted from longer intervals. To formally test this observation, all the resting-state data from all elderly participants during all time blocks was pieced together and separated into 1-second, 2-second, 3-second, and 4-second intervals before beta bursts were extracted. Since the same data was used for all intervals, it was expected that the burst rate within each interval to be the similar. However, **Figure 10 (left)** shows that this was not the case (see **Results** section **3.1**). Smaller intervals (1-second, 2-second) exhibited a significantly lower burst rate than longer intervals (3-second, 4-second).

This anomaly was very significant for this analysis since the pre-movement intervals were 1-second long, while all the other intervals of interest (rest, movement, post-movement) were 3-second long. By using this burst extraction algorithm as it is, a significant bias would be caused in the results which would likely lead to incorrect conclusions. It was thought that this issue arose from the fact that some bursts that lay at either one of the extremities of an interval cut off and thus fail to be detected due to not lasting more than 100ms above the threshold. To mitigate this problem, a small change was made to the burst extraction algorithm (**Figure 9**). While each interval of interest remained the same, the interval over which the bursts were extracted from was

elongated by 0.3s at each extremity. However, bursts only get detected if they start or end within the intervals of interest. This way, it is assumed that small intervals would no longer underrepresent the number of bursts detected since any bursts previously undetected at the extremities would now be detected. The term coined for this procedure is flexible intervals. As expected, **Figure 10 (right)** shows that by using flexible intervals, there is no longer any significant differences between any intervals.

Consequently, all the burst extraction performed in this study used flexible intervals. It was also ensured that no overlap between intervals of interest was made when computing the flexible intervals.

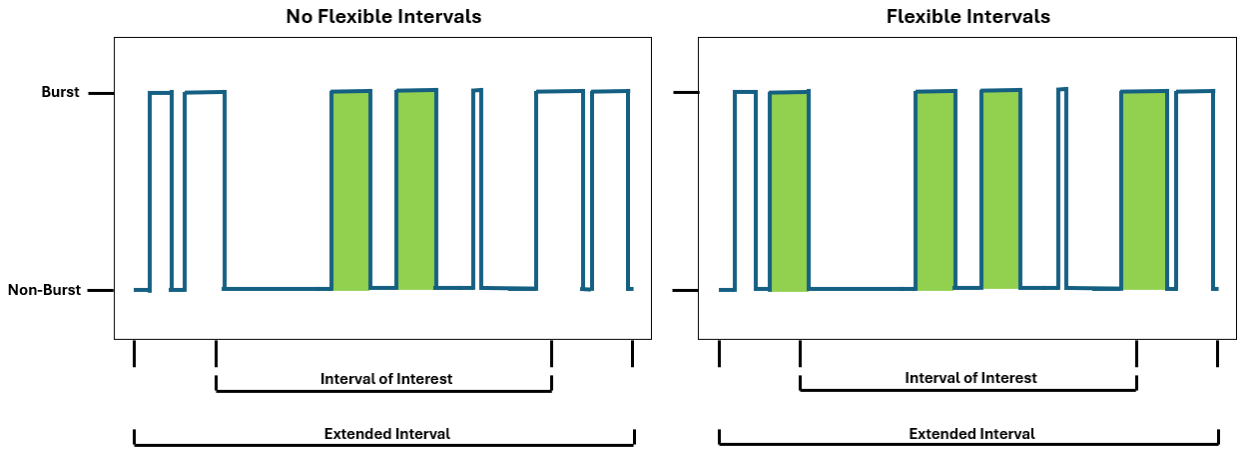

Figure 9. *Representation of the burst detection algorithm using flexible intervals. Detected bursts are marked in green. On the left, flexible intervals are not used, and the only bursts detected are those that are at least 100ms long within the interval of interest. On the right, flexible intervals are used, and bursts are screened within a larger extended interval. Only bursts that start or end within the interval of interest and are at least 100ms long are detected.*

2.3.3 Beta burst normalization

Most graphs are plotted using the raw values of beta burst characteristics and the units used are events/sec for rate, pV for amplitude, and ms for duration. However, some figures depict the burst characteristics normalized to baseline (**Figure 12**, **Supplementary Figures 2**, **3**, **4**). This

normalization was performed by subtracting each burst characteristic (rate, amplitude, duration) by the corresponding mean value extracted from the baseline time block. This normalization was made only for visualisation purposes and all statistical analyses were performed on the raw values of burst characteristics.

2.3.4 Beta power analysis for the stroke dataset

Beta power and MRBD analysis was already performed on the elderly dataset by Morales Fajardo (2023) and the same methodology is used on the stroke dataset to perform the beta power analysis.

The resting-state was separated into 5s segments, while the motor trials were epoched between 1 second prior to the trial initiation and 8 seconds post-trial initiation. These intervals were chosen for consistency with Morales Fajardo (2023). EEG signals were convolved using Morlet wavelets to obtain TF maps in the beta frequency band (15-29 Hz) for the C3 electrode. The TF maps were averaged within the frequency band and across all trials within a time block. To calculate the relative power or MRBD, the following formula was used:

$$MRBD\% = \frac{P(t) - B}{B}\ x\ 100\%$$

Where *P(t)* is the absolute power at time *t* and *B* is the baseline average power of the pre-movement phase calculated between 1s and 0.1s before trial initiation.

2.3.5 Statistical analysis

Bonferroni-corrected (Holm, 1979) Student's t-tests were used to assess differences in burst features between different movement intervals and across time as a result to different protocols of tACS stimulation during the rest and motor blocks in the elderly dataset. An α value of 0.05 was used as the cutoff for significance in these comparisons.

The Pearson correlation coefficient was calculated to determine whether there is a link between BBT scores and different beta power features in the elderly dataset.

No statistical analyses were performed on the stroke dataset due to an insufficient number of subjects.

CHAPTER 3: RESULTS

3.1 Flexible intervals

Figure 10 shows how beta bursts are underrepresented in smaller intervals (left) and how flexible intervals can alleviate this phenomenon (right).

When no flexible intervals were used, it was revealed that 1-second intervals have a statistically lower burst rate compared to the 2-second intervals ($p < 0.001$), 3-second intervals ($p < 0.001$), and 4-second intervals ($p < 0.001$). Moreover, the 2-second intervals have a statistically lower burst rate compared to the 3-second intervals ($p < 0.001$) and 4-second intervals ($p < 0.001$).

When beta burst analysis was performed using flexible intervals, no significant differences were found between the 4 intervals ($p > 0.05$).

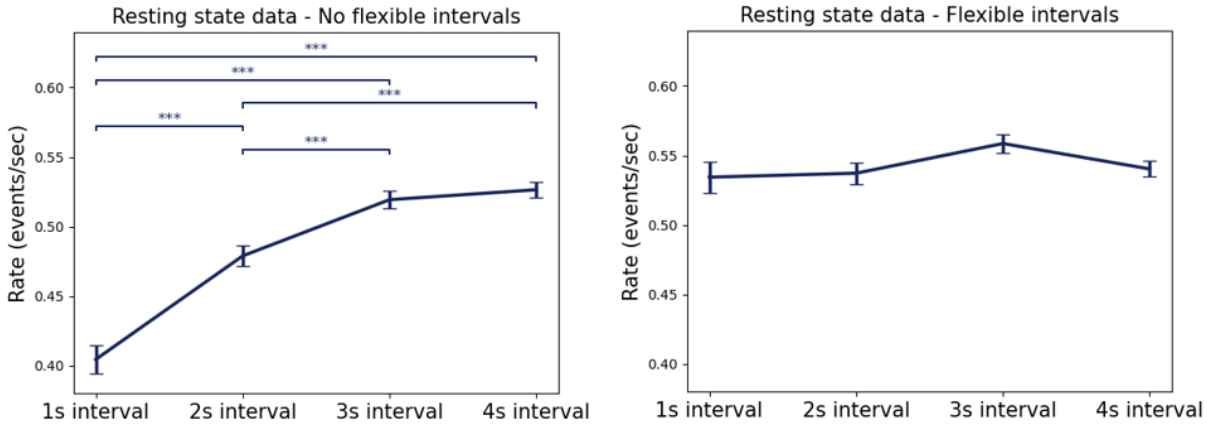

***Figure 10**. Comparison between using and not using flexible intervals. Burst rate plotted during the resting state period separated in 1s intervals, 2s intervals, 3s intervals, and 4s intervals during all time blocks extracted from the C3 electrode. Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

3.2 Elderly study

3.2.1 Behavioral assessment

The demographic data along with the behavioral assessment of the 15 participants from the elderly study are presented in **Table 1**.

Table 1. *Subject demographics and behavioral results in elderly participants (Morales Fajardo, 2023).*

		MEAN ± SD
AGE (YEARS)		69.8 ± 4.2
HANDEDNESS (/100)		94.6 ± 6.8
MINI-COG (/5 POINTS)		4.7 ± 0.49
BBT (BLOCKS/60 SEC)	Right Hand	56.4 ± 5.5
	Left Hand	57.2 ± 6.9
PPT (SEC)	Right Hand	13.4 ± 2.3
	Left Hand	12.0 ± 2.4
	Both Hands	10.4 ± 2.0
	Assembly	26.7 ± 5.1
HGS (KG)	Right Hand	32.7 ± 11.3
	Left Hand	30.7 ± 9.5

3.2.2 Movement-related beta burst changes

Figure 11 reveals how the different burst characteristics change during the 3 phases of the motor task in the sham session during the baseline time block extracted.

Burst Rate: A significant decrease in burst rate during the movement interval was observed compared to the pre-movement ($p < 0.05$) and the post-movement intervals ($p < 0.001$).

Burst Amplitude: A significant decrease in burst amplitude during the movement interval was observed compared to the pre-movement ($p < 0.001$) and the post-movement intervals ($p < 0.001$).

Burst Duration: A significant increase in burst duration was observed during the post-movement interval compared to the movement interval ($p < 0.01$).

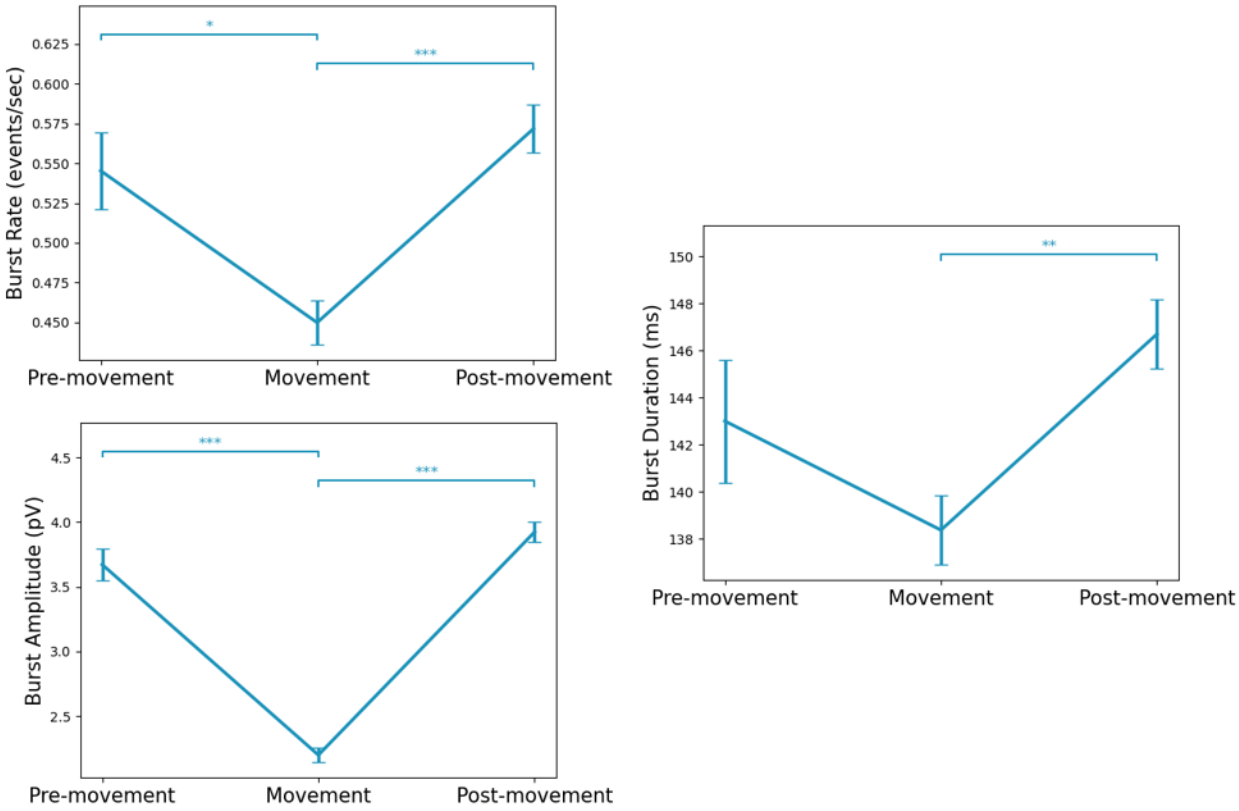

Figure 11. *Burst characteristics (rate, amplitude, duration) plotted during the motor task in the sham session during the baseline time block in elderly participants. Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

3.2.3 Effects of tACS stimulation protocols on resting state beta bursts

Figure 12 reveals the effects of different tACS stimulation protocols across time on the different burst characteristics extracted during the resting state period.

Burst Rate: No significant differences were observed between time blocks in any stimulation session ($p > 0.05$).

Burst Amplitude: A significant decrease in burst amplitude during the post-45 block was observed compared to the post-15 block in the sham stimulation session ($p < 0.001$). No other significant differences were observed ($p > 0.05$).

Burst Duration: No significant differences were observed between time blocks in any stimulation session ($p > 0.05$).

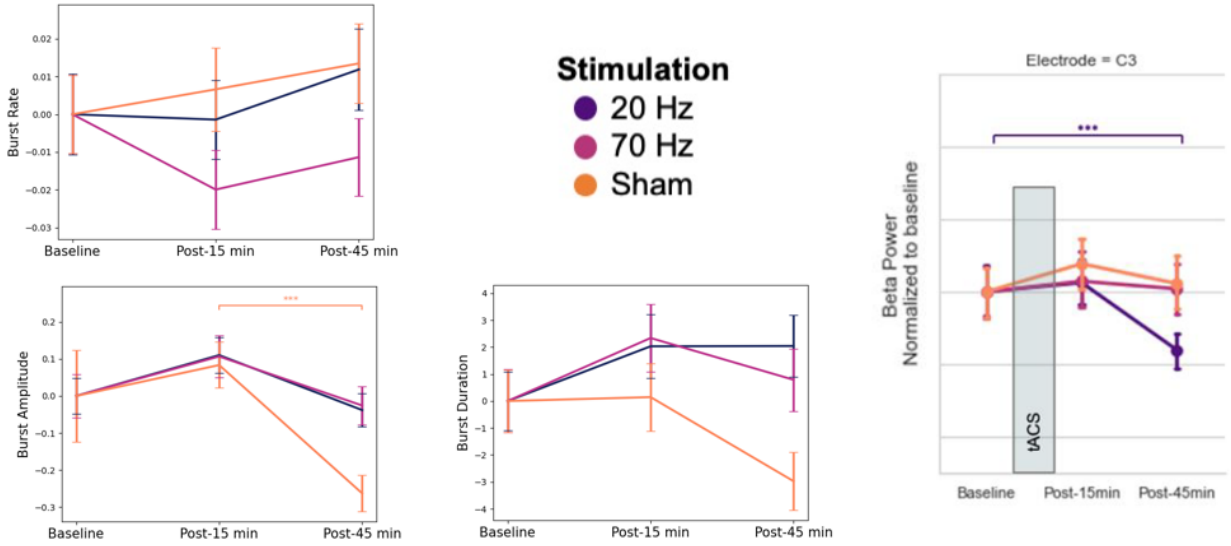

Figure 12. *Left: Burst characteristics (rate, amplitude, duration) normalized to baseline plotted from the resting state period in each stimulation session (20Hz, 70Hz, sham) across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation)* in elderly participants. *Right: Figure from Morales Fajardo (2023) of resting-state beta power normalized to baseline extracted from the C3 electrode in each stimulation session (20Hz, 70Hz, sham) across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

3.2.4 Effects of tACS stimulation protocols on beta bursts during movement

Figure 13 reveals the effects of sham stimulation across time on the different burst characteristics extracted from the movement interval during the motor task.

Burst Rate: No significant differences were observed between time blocks ($p > 0.05$).

Burst Amplitude: No significant differences were observed between time blocks ($p > 0.05$).

Burst Duration: No significant differences were observed between time blocks ($p > 0.05$).

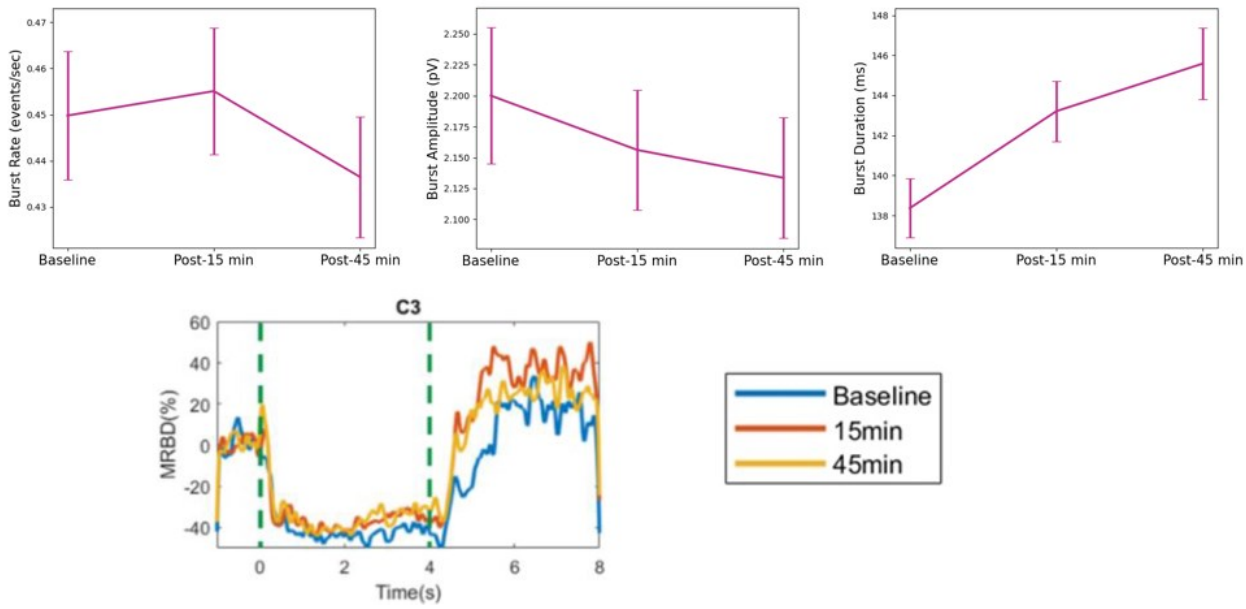

Figure 13. *<u>Up</u>: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the sham stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from the movement interval. <u>Down</u>: Figure from Morales Fajardo (2023) of the motor task % MRBD extracted from the C3 electrode in the sham stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

Figure 14 reveals the effects of 20 Hz tACS stimulation across time on the different burst characteristics extracted from the movement interval during the motor task.

<u>Burst Rate</u>: No significant differences were observed between time blocks ($p > 0.05$).

<u>Burst Amplitude</u>: No significant differences were observed between time blocks ($p > 0.05$).

<u>Burst Duration</u>: No significant differences were observed between time blocks ($p > 0.05$).

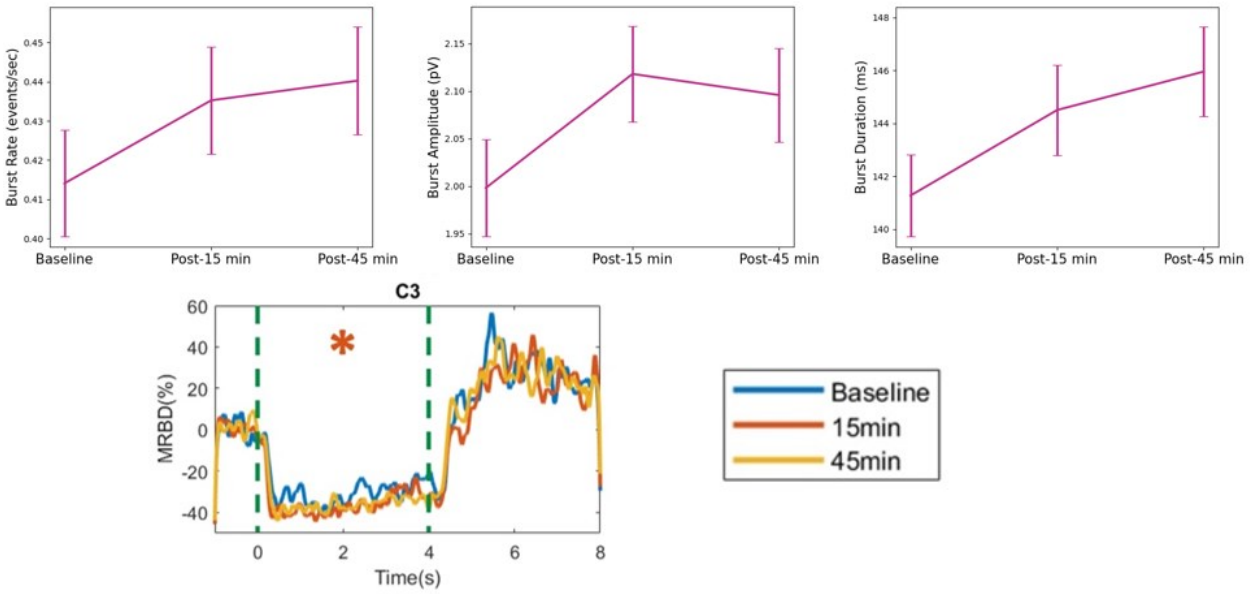

Figure 14. *Up: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the 20Hz tACS stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from the movement interval. Down: Figure from Morales Fajardo, 2023 of the motor task % MRBD extracted from the C3 electrode in the 20Hz tACS stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

Figure 15 reveals the effects of 70 Hz tACS stimulation across time on the different burst characteristics extracted from the movement interval during the motor task.

Burst Rate: No significant differences were observed between time blocks ($p > 0.05$).

Burst Amplitude: A significantly higher burst amplitude was observed during the post-45 block compared to the baseline block ($p < 0.01$).

Burst Duration: No significant differences were observed between time blocks ($p > 0.05$).

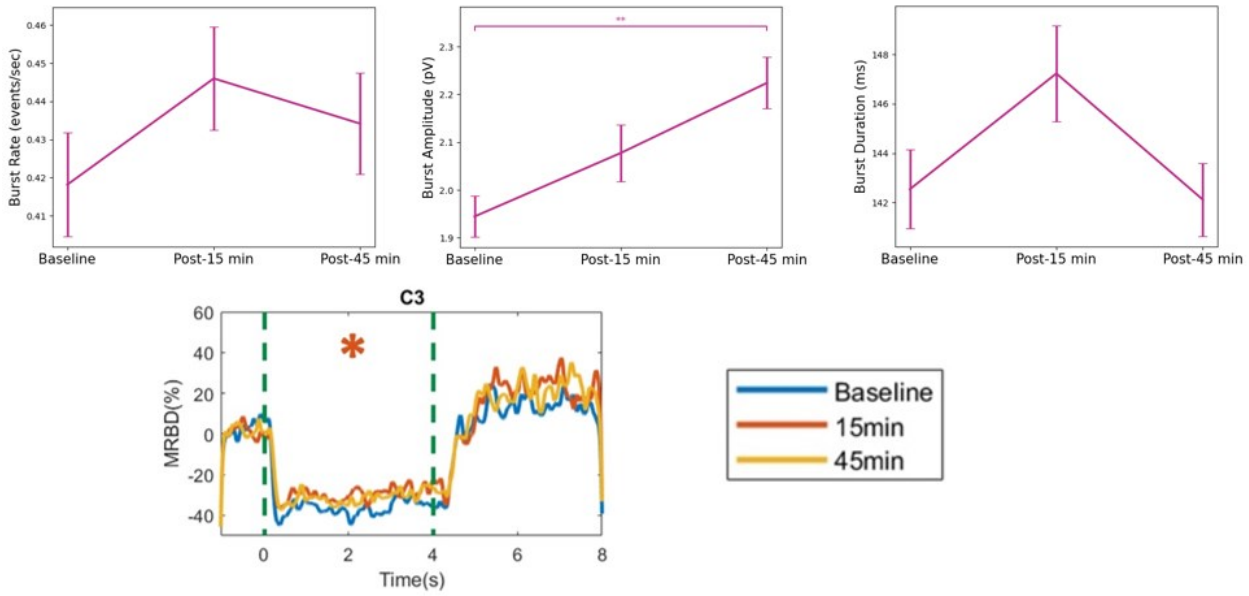

Figure 15. *Up: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the 70Hz tACS stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from the movement interval. Down: Figure from Morales Fajardo, 2023 of the motor task % MRBD extracted from the C3 electrode in the 70Hz tACS stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*

3.3 Stroke study

3.3.1 Behavioral assessment

The demographic data along with the behavioral assessment of the 3 participants from the stroke study are presented in **Table 2**. **Table 3** presents subject-specific data concerning the participants' stroke.

Table 2. *Subject demographics and behavioral results in stroke participants.*

		MEAN ± SD
AGE (YEARS)		65.0 ± 17.4
MINI-COG (POINTS)		4.7 ± 0.58
FMA-UL (/66)		54.3 ± 16.1
BBT (SEC)	Affected Hand	32.3 ± 28.0
	Unaffected Hand	56.7 ± 16.1
NHPT (BLOCKS/60 SEC)	Affected Hand	66.1 ± 51.9
	Unaffected Hand	20.4 ± 3.8
HGS (KG)	Affected Hand	28.3 ± 13.9
	Unaffected Hand	40.5 ± 11.2

Table 3. *Subject-specific stroke information.*

SUBJECT	STROKE LOCATION	AFFECTED SIDE	ASHWORTH SCALE	LINE CANCELLATION
1	Capsulo-thalamic	Left	N/A, 1+, 0, 0	-0.017
2	Cerebellum	Right	N/A, N/A, N/A, N/A	0
3	Subcortical	Right	0/0/0/0	0

** N/A: Not evaluated*

3.3.2 Effects of tDCS & tACS stimulation on beta bursts during movement

Table 4 presents the beta burst characteristics extracted from the movement interval during each stimulation session and each time block of the motor task. Due to a low number of participants (3) in the study, no statistical analysis was performed.

Table 4. *The mean and standard deviation (MEAN ± SD) of beta burst rate (events/sec), amplitude (pV), and duration (ms) for each time block (baseline, 15 min post-stimulation, 45 min post-stimulation) and each stimulation session (sham, tDCS, 70Hz tACS) extracted from the movement interval of the motor task.*

BASELINE	SHAM	TDCS	TACS
RATE	0.40 ± 0.25	0.42 ± 0.27	0.38 ± 0.30
AMPLITUDE	1.8 ± 0.87	1.7 ± 1.7	2.1 ± 0.70
DURATION	131.8 ± 33.4	130.5 ± 24.6	132.9 ± 27.8
POST-15 MIN			
RATE	0.46 ± 0.30	0.42 ± 0.27	0.41 ± 0.29
AMPLITUDE	1.4 ± 0.56	1.3 ± 0.66	1.7± 0.60
DURATION	145.3 ± 43.2	132.2 ± 27.5	135.5 ± 30.2
POST-45 MIN			
RATE	0.41 ± 0.30	0.37 ± 0.28	0.40 ± 0.28
AMPLITUDE	1.6 ± 0.66	1.2 ± 0.53	2.35 ± 0.90
DURATION	141.4 ± 35.9	133.3 ± 32.9	132.7 ± 26.2

3.4 Comparison between the elderly and stroke studies

3.4.1 Resting state comparison

Table 5 compares the beta power and beta burst characteristics between the healthy elderly participants and the stroke participants extracted from the resting state period during the sham stimulation session and baseline time block. Due to a low number of participants (3) in the stroke study, no statistical analysis was performed.

Table 5. *The mean and standard deviation (MEAN ± SD) of beta power (pV^2/Hz) and beta burst rate (events/sec), amplitude (pV), and duration (ms) extracted from the resting state period* in *the sham stimulation session* during the *baseline time block for healthy elderly participants and stroke participants.*

RESTING STATE	OLD PARTICIPANTS	STROKE PARTICIPANTS
BETA POWER	0.17 ± 0.15	0.046 ± 0.012
BURST RATE	0.52 ± 0.34	0.40 ± 0.28
BURST AMPLITUDE	3.7 ± 5.1	1.7 ± 0.61
BURST DURATION	148.9 ± 47.9	133.8 ± 30.1

3.4.2 Movement intervals comparison

Figure 16 compares the relative and absolute beta power between the healthy elderly participants and the stroke participants during the sham stimulation session and baseline time block of the motor task. Due to the low number of participants (3) in the stroke study, no statistical analysis was performed.

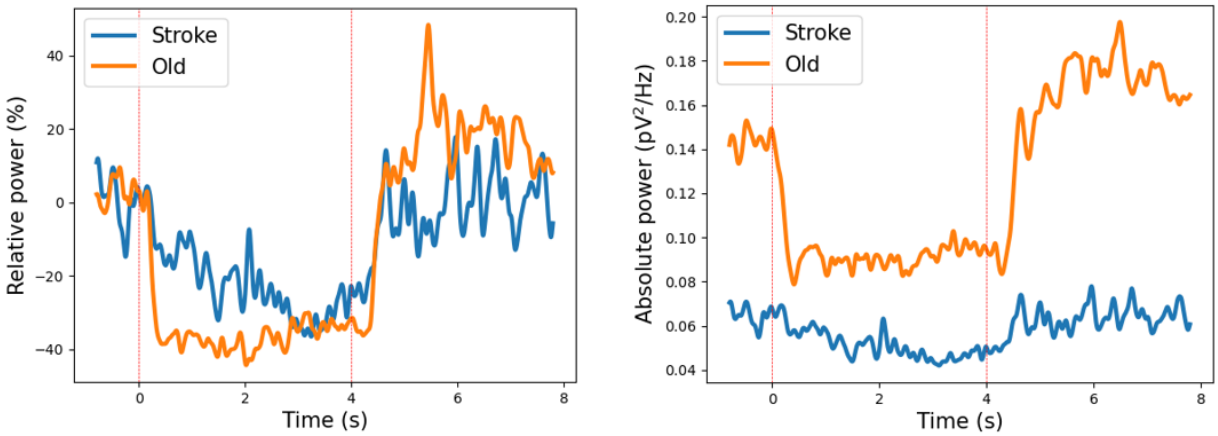

Figure 16. *Absolute and relative beta power plotted during the motor task in the sham stimulation session during the baseline time block in healthy elderly and stroke participants. The data from the elderly participants was obtained from Morales Fajardo (2023).*

Table 6 compares the beta burst characteristics between the healthy elderly participants and the stroke participants extracted from each movement interval during the sham stimulation session and baseline time block of the motor task. Due to a low number of participants (3) in the stroke study, no statistical analysis was performed.

Table 6. *The mean and standard deviation (MEAN ± SD) of beta burst rate (events/sec), amplitude (pV), and duration (ms) extracted from each movement interval of the motor task* in *the sham stimulation session* during the *baseline time block for healthy elderly and stroke participants.*

PRE-MOVEMENT	OLD PARTICIPANTS	STROKE PARTICIPANTS
RATE	0.55 ± 0.57	0.35 ± 0.48
AMPLITUDE	3.6 ± 2.1	2.1 ± 0.92
DURATION	143.0 ± 44.8	137.5 ± 30.1
MOVEMENT		
RATE	0.45 ± 0.32	0.40 ± 0.25
AMPLITUDE	2.2 ± 1.5	1.8 ± 0.9
DURATION	138.4 ± 39.6	131.8 ± 33.4
POST-MOVEMENT		
RATE	0.57 ± 0.35	0.44 ± 0.27
AMPLITUDE	3.9 ± 2.4	2.3 ± 1.3
DURATION	146.7 ± 44.6	141.9 ± 40.1

3.4.3 Association between BBT scores and beta power during rest and movement

Figure 17 comprises 4 scatter plots of the BBT scores and different beta power metrics (resting beta power, pre-movement beta power, movement beta power, % MRBD) in the healthy elderly participants and the stroke participants in the sham stimulation session during the baseline time block of the motor task.

The Pearson correlation coefficient was calculated in elderly subjects and it revealed no correlation between motor scores and resting beta power ($r = 0.23$, $p = 0.41$), no correlation between motor scores and pre-movement beta power ($r = 0.26$, $p = 0.35$), no correlation between motor scores and movement beta power ($r = 0.36$, $p = 0.19$), and no correlation between motor scores and % MRBD ($r = 0.09$, $p = 0.74$). No analysis was performed on stroke participants due to an insufficient number of subjects (3).

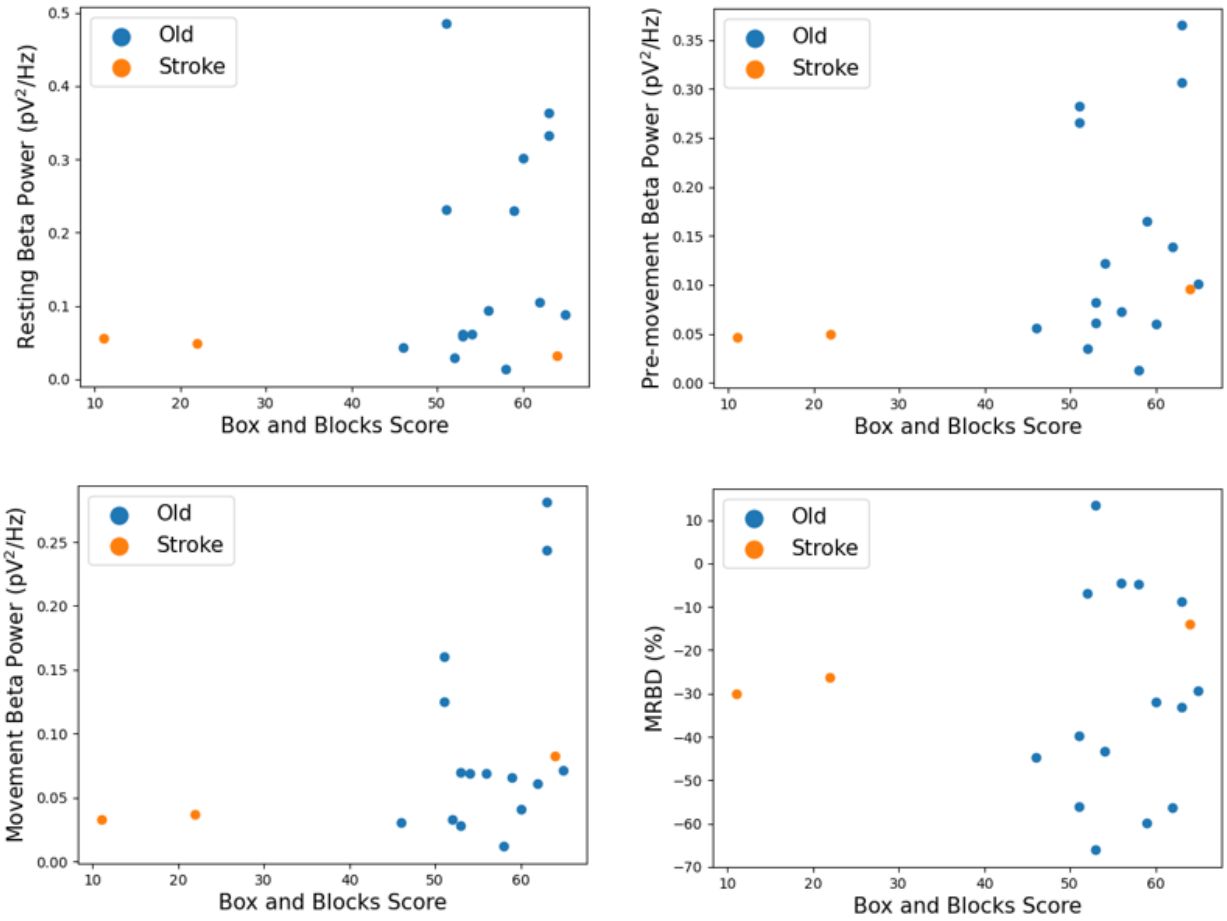

Figure 17. *Scatter plots of the BBT scores and resting state beta power (top left), pre-movement beta power (top right), movement beta power (bottom left), and % MRBD (bottom right) extracted from the motor task in the sham stimulation session during the baseline time block in healthy elderly and stroke participants.*

CHAPTER 4: DISCUSSION

This study aimed to determine the link between beta bursts and beta power, quantify the effects of 20 Hz and 70 Hz tACS stimulation on beta burst characteristics in elderly individuals, and assess whether these effects persist after stimulation. This study also aimed to compare the beta power and burst characteristics between elderly and stroke individuals in an exploratory analysis. By extracting the beta bursts from the same dataset that was used by Morales Fajardo (2023) to perform beta power analysis, a clearer comparison can be made between beta bursts characteristics and beta power. Many of the results of Morales Fajardo (2023) were focused around the C3 electrode which lies on top of the left sensorimotor areas. Moreover, since this study used HD tACS stimulation, the C3 electrode also lies on top of the brain region receiving the largest amount of stimulation (see **Methods** section **2.1.3**). Consequently, all the beta bursts in this study were extracted from the C3 electrode.

Firstly, beta bursts were characterized during the 3 phases of the motor task (pre-movement, movement, post-movement). Both rate and amplitude showed a significant decrease during the movement phase, followed by a significant increase upon movement termination. Burst duration was only significantly lower during the movement phase compared to the post-movement phase.

Next, the effects of 20 Hz and 70 Hz tACS stimulation on beta bursts were quantified during rest and movement. No effects of stimulation were observed on any burst characteristics extracted from the resting state. As for the effects of stimulation observed during the movement phase of the motor task, 70 Hz tACS stimulation caused a significant increase in burst amplitude 45 minutes post-stimulation compared to the baseline values. No other effects were observed from sham and 20 Hz tACS stimulation.

Finally, an exploratory analysis was performed on an initial dataset of stroke participants to have a preliminary comparison with the results obtained from the elderly dataset. However, due to the low number of participants in this study, no statistical analyses were performed. The most significant observation was that healthy elderly participants seem to exhibit more than twice as much beta power at rest and during movement compared to stroke participants, as well as a higher burst rate and amplitude during both rest and movement. However, the % MRBD during the motor task seems to be similar between the two groups.

4.1 Beta burst extraction

Before further discussing the results obtained in this study, it should be addressed that beta bursts are still a relatively new concept and the methodology of extracting these bursts has not been standardized yet. Researchers use different algorithms to extract bursts and there is no clear consensus on which method is the best. For instance, several publications applied the 75th percentile method that was used in the current analysis (He *et al.*, 2020; Kohl *et al.*, 2024; Tinkhauser *et al.*, 2017a; Tinkhauser *et al.*, 2017b; Yu *et al.*, 2021). However, other researchers used different methodologies to extract bursts. For example, Little *et al.* (2019) used a similar thresholding approach, except that instead of using the 75th percentile, they used a threshold corresponding to 1.75 standard deviations above the median beta power (~ 95th percentile). Shin *et al.* (2017) and Wessel (2020) used a threshold value of 6 X median beta power. Other researchers investigated algorithms that do not use a thresholding method but instead use data-driven models such as the Hidden Markov models (Kohl *et al.*, 2024; Seedat *et al.*, 2020).

The reason why this is important is because while beta bursts are thought to be at the origin of beta oscillatory activity in relation to movement production, using a suboptimal or "wrong"

methodology to extract bursts might lead to an unclear relationship between beta bursts and beta power, and the conclusions drawn might be incorrect or incomplete. This point might explain some of the unexpected results obtained in this study that will be discussed in more detail later.

The burst extraction method applied in this study calculated the 75th percentile from the baseline beta power as the threshold. However, even when using this method, there are multiple parameters that could be modified, leading to a difference in the bursts identified. For instance, the baseline used to calculate the 75th percentile could be modified. In this study, the baseline was always calculated from the segment the bursts were extracted from. However, using a different baseline calculated from the resting state signal for both the rest and motor data might also be an option worth investigating. Moreover, using the 75th percentile is an arbitrary value that could be easily modified to 70th percentile or 80th percentile, which would also lead to a different number of bursts identified.

Another aspect to consider is that even after the bursts are identified, the burst characteristics extracted play a crucial role as it can be seen in the results. The characteristics extracted in this study were the rate, maximum amplitude, and duration, which is similar to other studies (Shin *et al.*, 2017; Yu *et al.*, 2021). The behavior of each characteristic exhibited some differences from one another in the analyses of this study. However, there are other characteristics that could have been extracted and might have been equally interesting to analyse. The fractional occupancy (% of total time with bursts present) and the average burst amplitude (in contrast to the maximum burst amplitude) are two examples of such characteristics (Kohl *et al.*, 2023).

Finally, an important result obtained in this study that was not part of any hypotheses or objectives was that when using the 75th percentile extraction method on small intervals (< 3sec), bursts are severely underestimated as it can be seen in **Figure 10**. It is unknown whether this

phenomenon happens when using other types of burst extraction algorithms as it was not tested. This can become a significant problem if bursts are extracted from intervals of different sizes for analysis. However, one method that was developed to remove this bias is through the use of flexible intervals (see **Methods** section **2.3.2**). Thus, it is recommended to use flexible intervals when extracting bursts from small intervals and/or intervals of different sizes.

4.2 Effects of active movement of the hand on beta burst characteristics

One of the objectives of this study was to understand the association between beta bursts and beta power, and more specifically, understand which burst characteristics follow a similar trend as the beta power oscillations. It was hypothesized that the burst amplitude would be closely related to beta power patterns, followed by burst rate. In contrast, burst duration was expected to be the least significantly correlated characteristic to beta power. This assumption was made based on previous literature from a similar study in which beta bursts were extracted from MEG data in elderly participants while they performed a motor task with their right hand (Chatterjee, 2022). The results from this study showed that the burst amplitude during the movement phase is lower than both the amplitude during the resting state and the amplitude during the post-movement phase. The burst rate during the movement phase was only lower than the rate during the post-movement phase, but not the resting state (Chatterjee, 2022). As for burst duration, there were no consistent significant changes across the movement phases. As the MRBD is characterized by a highly significant drop in beta power during active movement, followed by a rebound upon movement termination (Pfurtscheller & Lopes da Silva, 1999; Stancák Jr & Pfurtscheller, 1995), it can be inferred that burst amplitude followed the MRBD pattern more closely, burst rate followed the

MRBD pattern partially, while burst duration had almost no association with the MRBD pattern (Chatterjee, 2022).

The first beta power pattern that was compared to burst characteristics in this study was the MRBD in order to assess whether the results from the above-mentioned study (Chatterjee, 2022) can be reproduced with beta bursts extracted from EEG data instead of MEG. The results from **Figure 11** show that both burst rate and burst amplitude were significantly lower in the movement phase compared to the pre-movement and post-movement phases, while the burst duration was significantly lower in the movement phase compared to the post-movement phase. These results were slightly unexpected as they do not perfectly correlate with the results from Chatterjee (2022). Thus, in order to test the consistency of these results, two more motor blocks were introduced for this comparison of bursts characteristics across the 3 movement phases in **Supplementary Figure 1**. In order to ensure that brain stimulation does not play a part in interpreting these results, the other 2 motor blocks introduced are both from the sham stimulation session (15 min post-stimulation and 45 min post-stimulation). Interestingly, the results from both these blocks show that burst amplitude during the movement phase was significantly lower than the amplitude during the pre-movement and post-movement phases, similar to what was observed for the baseline block. However, the burst rate during the movement phase was lower than the rate during the post-movement phase, but not different from the rate during the pre-movement phase. Moreover, burst duration did not significantly differ between the movement phases in these two motor blocks. Consequently, if all three motor blocks are considered, the results obtained correspond well with the results obtained by Chatterjee (2022) in that burst amplitude closely relates to the MRBD pattern, followed by burst rate. Finally, burst duration does not seem to relate to the MRBD pattern in a consistent manner.

4.3 Effects of tACS stimulation on beta burst characteristics

After characterizing the relationship between beta burst characteristics and MRBD, the next objective of this study was to determine the effects of 20 Hz and 70 Hz tACS stimulation on beta burst characteristics and compare them with the results obtained from beta power analysis by Morales Fajardo (2023). However, it was interesting to see that there was no clear association between burst characteristics and beta power in the context of stimulation. For instance, when looking at the effects of stimulation on the resting state beta bursts, the only significant difference is that the burst amplitude 45 min post-stimulation was significantly lower than the amplitude at 15 min post-stimulation in the sham stimulation session. This result is unexpected in and of itself given that the sham stimulation was not expected to produce any effects in the brain. In contrast, beta power analysis showed a significantly lower beta power 45 min post-stimulation compared to baseline in the 20 Hz stimulation session (Morales Fajardo, 2023). Next, the effects of brain stimulation on beta bursts and beta power were compared during the movement phase of the motor task. No significant differences were obtained neither in the beta bursts nor in the beta power (Morales Fajardo, 2023) in the sham stimulation session. This result was expected as sham stimulation is not supposed to produce any significant effects. In the 20 Hz tACS stimulation session, no significant difference was obtained in the burst characteristics, but a significantly lower beta power was obtained 15 min post-stimulation compared to baseline (Morales Fajardo, 2023). Finally, in the 70 Hz tACS stimulation session, a significantly higher burst amplitude was observed 45 min post stimulation compared to baseline, while a significantly higher beta power was obtained 15 min post stimulation compared to baseline (Morales Fajardo, 2023). Consequently, none of the burst characteristics seem to follow the beta power trends in the context of stimulation.

There are several possible explanations for these results. Firstly, as mentioned in section **4.1**, it is possible to have used a suboptimal burst extraction algorithm or to not have extracted potentially more significant burst characteristics such as the fractional occupancy or the average burst amplitude (Kohl *et al.*, 2023). Another possibility is that the stimulation effects were not strong enough to produce clear effects in beta bursts but were barely enough to produce clear effects in beta power analysis. It is also possible that the data was very noisy and beta power analysis is more resistant to noise than beta burst analysis. This phenomenon may possibly occur due to implementing beta power analysis by averaging across multiple trials from the beginning of the analysis, thus reducing the noise in the signal, while the bursts are extracted from each individual trial, and thus they are more prone to random fluctuations in the data. It is plausible that stronger and more consistent effects would be observed while the stimulation is ongoing. However, as mentioned later in section **4.5**, it was not possible to extract bursts from the stimulation time block due to excessive artifacts caused by tACS.

Finally, the effects of stimulation on beta bursts were also quantified for the pre-movement and post-movement intervals even though it was not part of the objectives, and no comparison was made with beta power results since Morales Fajardo (2023) did not look into the effects of stimulation on these movement intervals. The reason why these effects are presented is because the activity within the post-movement interval is related to PMBR, which is known to be related to motor skill learning (Espenhahn *et al.*, 2019; Espenhahn *et al.*, 2020). **Supplementary Figures 2, 3, 4** show the effects across time of sham, 20 Hz tACS, and 70 Hz tACS respectively on all three movement intervals (pre-movement, movement, post-movement). No significant results were obtained within the pre-movement interval for any stimulation protocol, while for the post-movement interval, the only significant result is that burst amplitude was significantly higher 15

minutes post-stimulation compared to baseline in the 20 Hz tACS session. Although it is hard to draw any definitive conclusions, it is possible that different tACS protocols may affect different movement intervals since 20 Hz tACS caused an increased burst amplitude during the post-movement interval, while 70 Hz tACS caused an increased burst amplitude during the movement interval. However, more research is required to see if these results can be consistently replicated.

4.4 Exploratory analysis using a preliminary stroke dataset

Due to the low number of participants (3) in the stroke study at the moment, no statistical analyses were performed, and all the results are descriptive to assess potential similarities and differences with the elderly dataset. Thus, these comparisons should not be treated as definitive results until the sample size of stroke participants is increased.

When looking at the effects of anodal tDCS and 70Hz tACS on burst characteristics during movement, it is observed that tDCS may cause a decrease in burst amplitude 15 min and 45 min post-stimulation, while 70Hz tACS may cause an increase in burst amplitude 45 min post-stimulation according to **Table 4**. The % MRBD data was plotted for each subject separately in **Supplementary Figures 5**, **6**, and **7** to illustrate the effects of sham, tDCS, and 70Hz tACS stimulation respectively. However, no clear trend is seen across all participants.

When comparing the elderly dataset to the stroke dataset, the most striking difference observed is that elderly individuals seem to have more than two times higher beta power and a higher burst rate and amplitude compared to stroke individuals at rest and during all movement intervals as seen in **Table 5**, **Table 6**, and **Figure 16**. This result is expected since elderly individuals are known to have a higher overall beta power than controls (Xifra-Porxas et al., 2019), while stroke individuals are known to have a lower overall beta power than controls (Kulasingham

et al., 2021). So, when comparing the elderly individuals to the stroke individuals, it is expected to see this striking difference. Interestingly, although elderly individuals seem to have a significantly higher beta power than stroke individuals, the % MRBD in the two groups is remarkably similar as it can be observed in **Figure 16**. However, when observing the absolute values, it is clear that in reality, stroke individuals desynchronize way less than elderly individuals and the reason for the similarity in the % MRBD between the two groups is due to the fact that elderly subjects exhibit a higher overall beta power.

By comparing the behavioral results of elderly and stroke participants in **Table 1** and **Table 2**, it is observed that stroke participants had notably worse results with their affected hand. This is expected as stroke is known to cause severe motor deficits (Hankey *et al.*, 2002; Schlaug *et al.*, 2008). The drastic difference between elderly individuals and stroke individuals in terms of both beta power and behavioral results raised the question of whether behavioral results may be correlated to beta power metrics. To test this hypothesis, several beta power metrics were chosen: resting beta power, pre-movement beta power, movement beta power, and % MRBD. The behavioral test chosen for comparison is the BBT due to being a common test for both elderly and stroke individuals as well as due to not having remarkably different results between male and female participants as the HGS test does. However, the results show no significant correlation between BBT results and any of the beta power metrics for elderly participants. Moreover, the scatter plots in **Figure 17** make it unclear whether stroke participants show such a correlation as well. Furthermore, it seems that the beta power in stroke participants may not be lower than all healthy elderly participants. In fact, it seems that elderly participants show a wide range of beta power values and the stroke participants' beta power is similar to the beta power of healthy elderly

participants who exhibit a relatively low beta power. Thus, no conclusions should be drawn before increasing the sample size of stroke participants.

4.5 Further limitations

One clear limitation in this study is the small dataset of stroke participants which didn't allow for any statistical analyses to be made. However, it could be argued that the sample size for the elderly dataset is also rather small. Unfortunately, this is a common occurrence in EEG studies and small sample sizes are known to undermine the statistical power of these studies and lead to increased false-positive effects (Vozzi *et al.*, 2021). The small sample size may have prevented clearer effects of stimulation on beta burst characteristics, as well as a clearer association between beta bursts and beta power in the context of stimulation.

Another limitation in this study is that the data recorded during stimulation could not be used due to considerable stimulation artifacts. It is expected that the more pronounced effects of stimulation on beta oscillatory activity are observed during the stimulation motor block. A member of our laboratory is currently working on developing an algorithm to remove stimulation artifacts to make the data recorded during the stimulation usable (Yan *et al.*, 2022). When the data recorded during the stimulation blocks will be analysed, it is possible that beta bursts and beta power will be more strongly associated with each other.

CHAPTER 5: CONCLUSION

The aim of this study was to determine the relation between beta bursts and averaged beta power, determine the effects of 20 Hz and 70 Hz tACS stimulation on beta bursts in elderly participants, and compare the beta bursts and beta power between older and stroke subjects. It was found that burst amplitude is the burst characteristic that is the most closely related to MRBD, showing a lower amplitude during the movement interval compared to the pre-movement and post-movement intervals. Burst rate followed a similar pattern, but not as strongly. Finally, burst duration seemed very weakly related to averaged beta power.

In terms of effects of tACS stimulation, the only effect found is that 70 Hz tACS stimulation caused a significant increase in burst amplitude 45 minutes post-stimulation compared to the baseline values. No effects were found for 20 Hz tACS stimulation. These results were unexpected, given that the MRBD analysis performed on the same dataset showed an increased MRBD 15 minutes after 20 Hz tACS and a decreased MRBD 15 minutes after 70 Hz tACS (Morales Fajardo, 2023). It is possible that burst rate and amplitude might not be as closely related to MRBD as expected. It is also possible that a better burst extraction algorithm is needed to observe consistent results. Nevertheless, further research is needed to address these limitations and inconsistencies in the results.

Finally, the elderly dataset was compared to an initial stroke dataset to visualize differences in beta bursts and beta power. Although no statistical analysis was performed, the most important difference observed between the two groups is that healthy older participants showed a much higher overall beta power, burst rate, and burst amplitude compared to stroke subjects. Although there are several studies performed both on stroke and elderly subjects looking at the MRBD present in these individuals, no study to our knowledge directly compared the two groups and

reported such a noteworthy difference in the beta power and MRBD. It is possible that in order to improve the oscillatory rhythms in elderly and stroke individuals to resemble a more normal pattern seen in younger controls, different protocols of NIBS should be applied. For older subjects, a brain stimulation protocol capable of reducing the overall beta power and burst characteristics would be preferable, while for stroke survivors, a protocol that can increase the overall beta oscillatory rhythms would be desirable.

The current study contributes to our knowledge of how NIBS affects brain activity in elderly and stroke individuals. This knowledge can contribute to better determining which NIBS parameters to use in future studies. The results will be ultimately used to design optimal NIBS protocols as part of a closed-loop neurofeedback approach adapted to each individual's intrinsic brain oscillations to improve individuals' recovery of motor functions. Such technology could improve their quality of life. The societal impact of this project is to contribute to reducing the cost of rehabilitation by optimizing recovery on an individual basis and increasing the independence of individuals presenting motor deficits, such as older individuals, stroke survivors, and Parkinson's patients.

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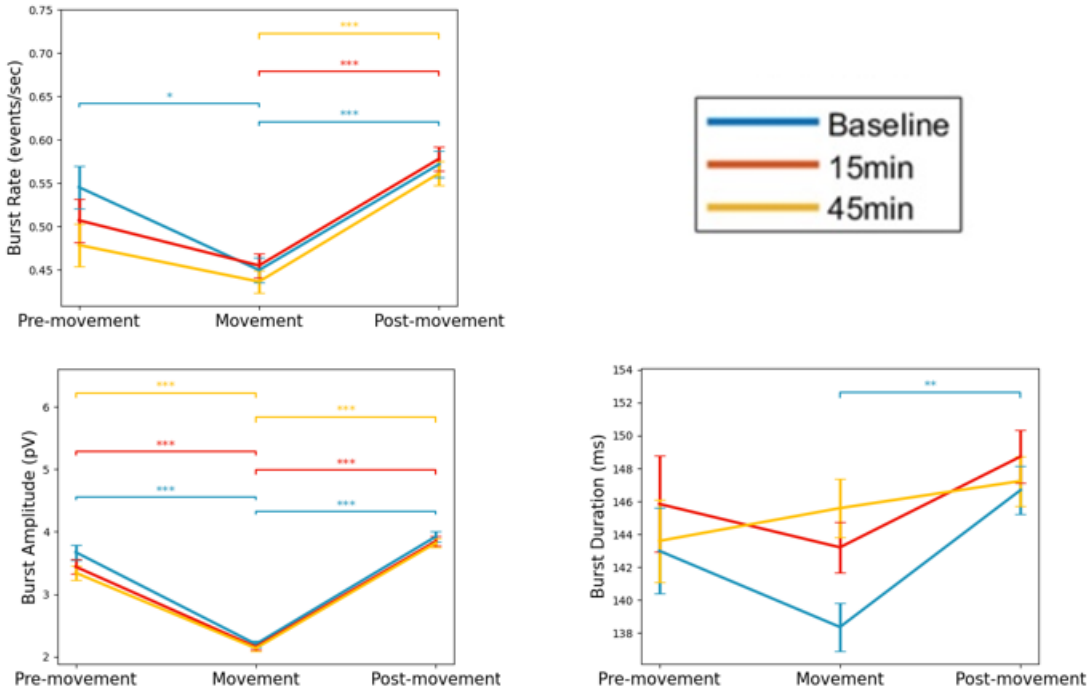
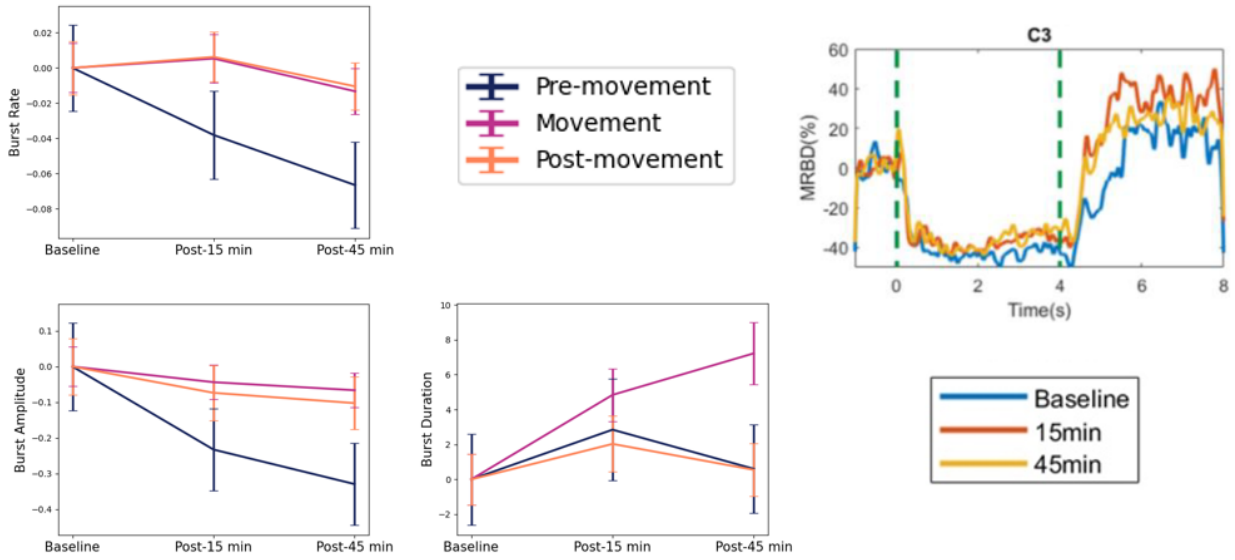
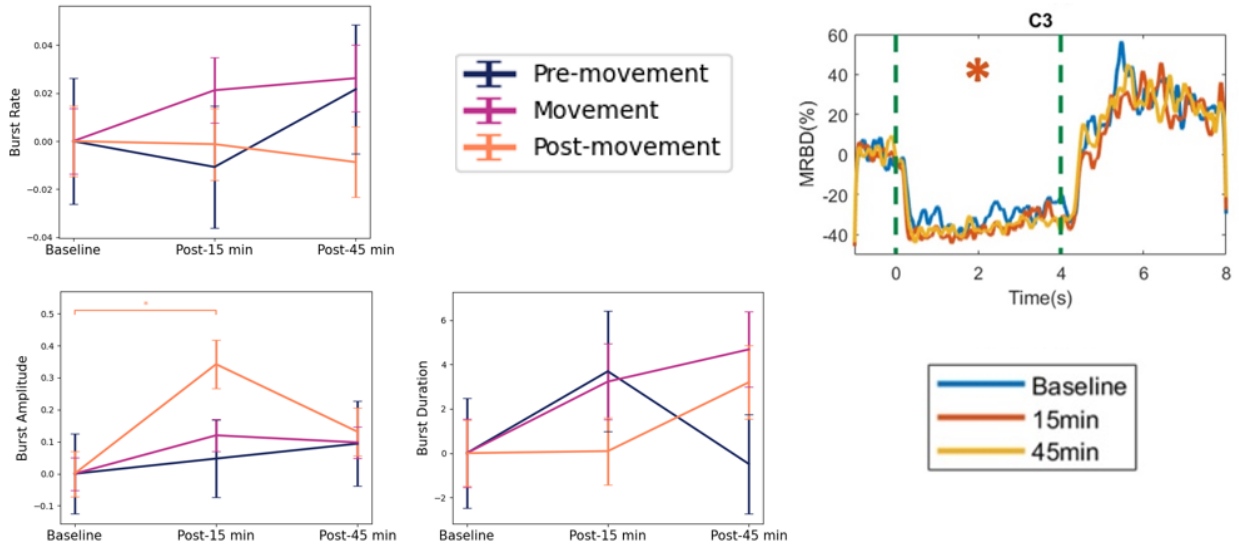
SUPPLEMENTARY FIGURES



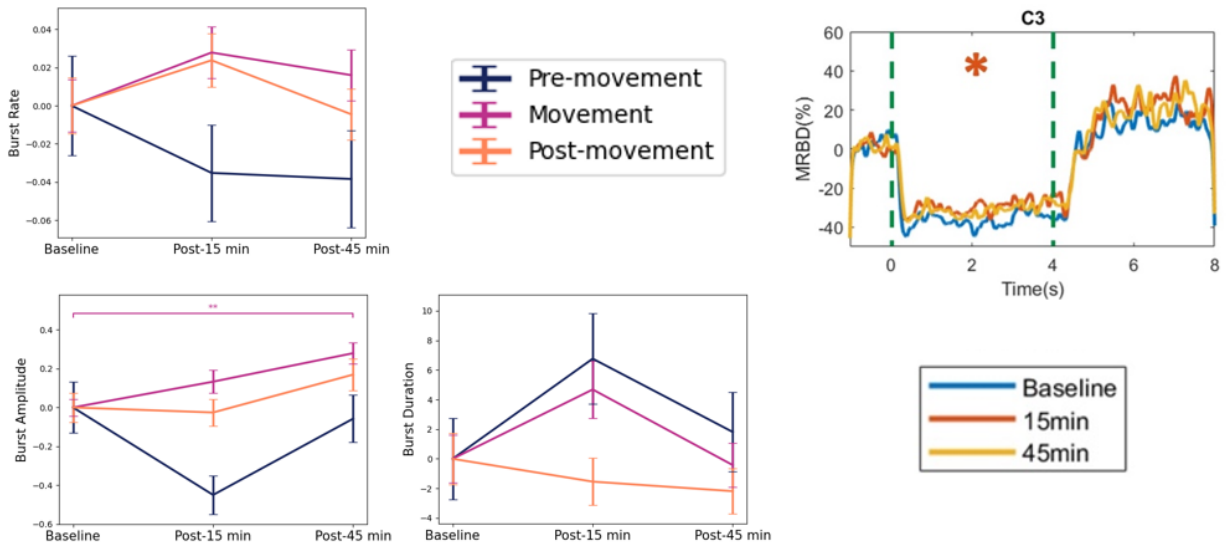
Supplementary Figure 1. *Burst characteristics (rate, amplitude, duration) plotted during the motor task in the sham stimulation session during the baseline, post-15 min, and post-45 min time blocks extracted from the C3 electrode in elderly participants. Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*



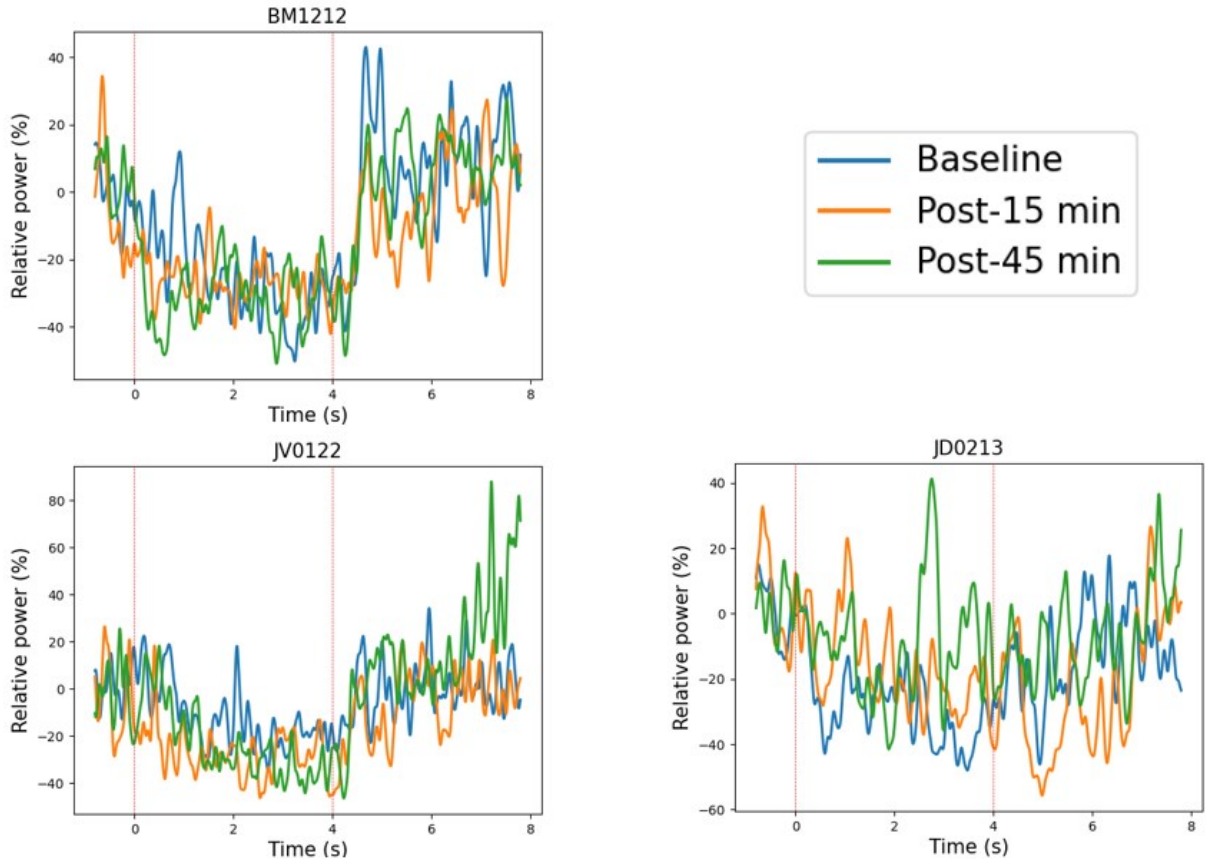
Supplementary Figure 2. *<u>Left</u>: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the sham stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from all the movement intervals (pre-movement, movement, post-movement) in elderly participants. <u>Right</u>: Figure from Morales Fajardo, 2023 of the motor task % MRBD extracted from the C3 electrode in the sham stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*



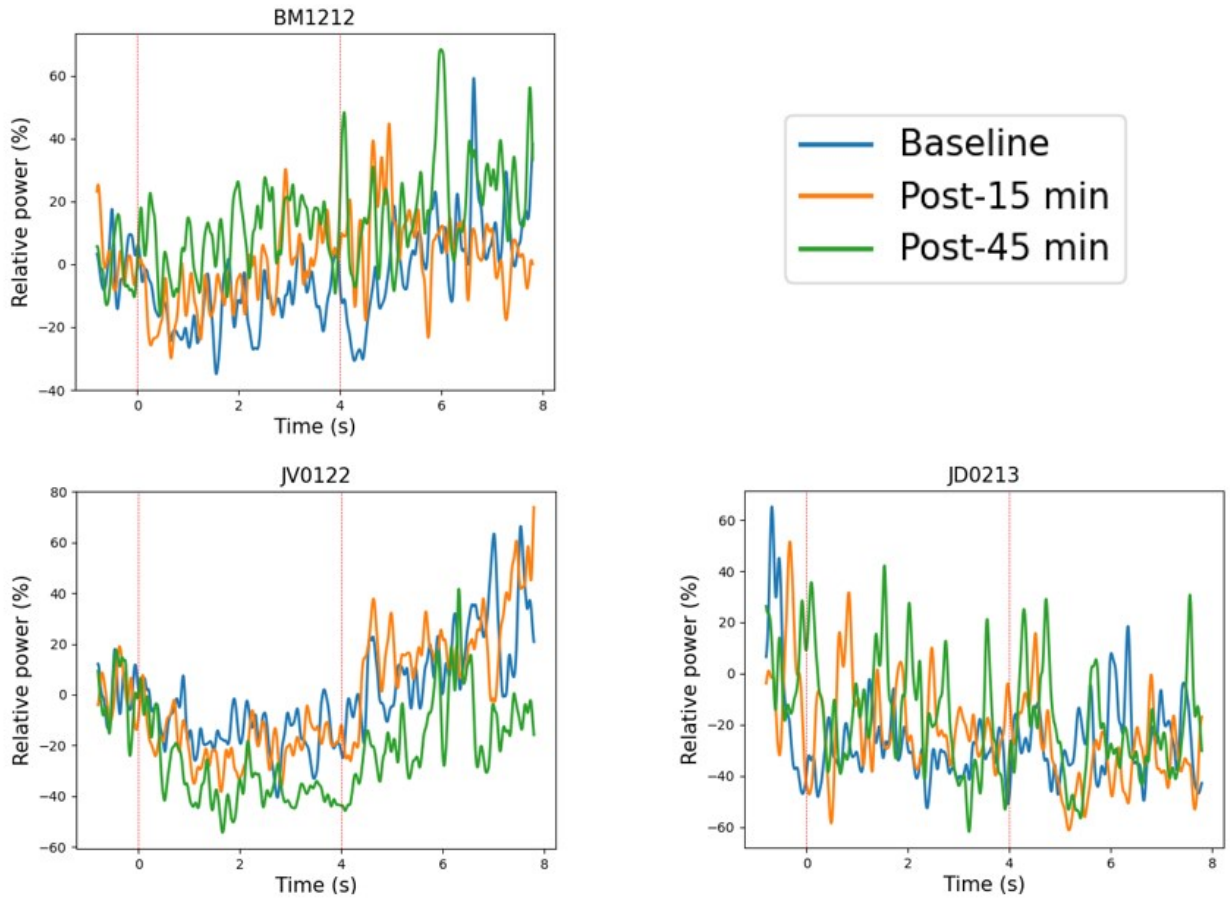
Supplementary Figure 3. *Left: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the 20 Hz tACS stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from all the movement intervals (pre-movement, movement, post-movement) in elderly participants. Right: Figure from Morales Fajardo, 2023 of the motor task % MRBD extracted from the C3 electrode in the 20 Hz stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*



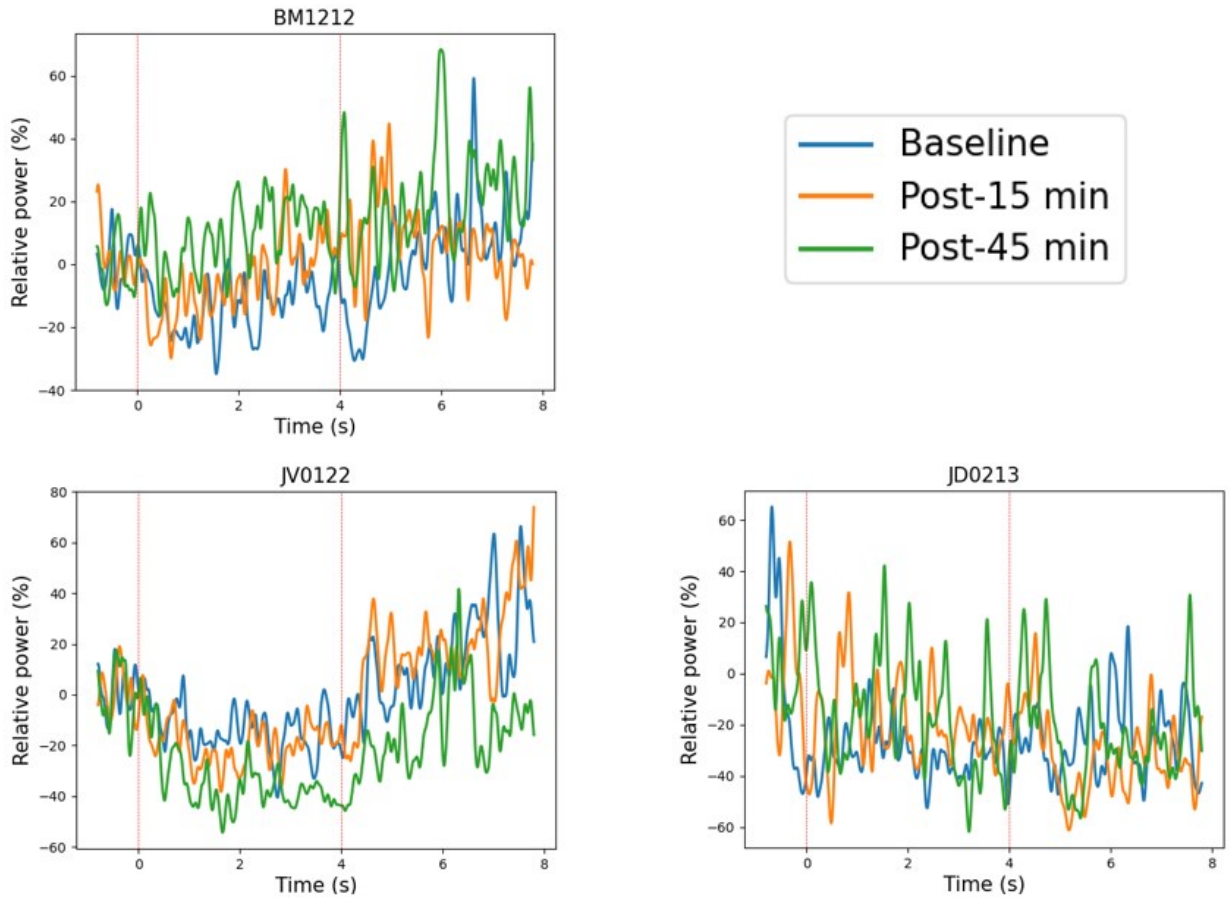
Supplementary Figure 4. *<u>Left</u>: Burst characteristics (rate, amplitude, duration) plotted from the motor task in the 70 Hz stimulation session across three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation) extracted from all the movement intervals (pre-movement, movement, post-movement) in elderly participants. <u>Right</u>: Figure from Morales Fajardo, 2023 of the motor task % MRBD extracted from the C3 electrode in the 70 Hz stimulation session for three time blocks (baseline, 15 min post-stimulation, 45 min post-stimulation). Error bars represent standard error. Bonferroni-corrected Student's t-test *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.*



Supplementary Figure 5. *% MRBD plotted during the motor task for the sham stimulation session during the baseline, 15 min post-stimulation, and 45 min post-stimulation time blocks extracted for each stroke participant.*



Supplementary Figure 6. *% MRBD plotted during the motor task for the tDCS stimulation session during the baseline, 15 min post-stimulation, and 45 min post-stimulation time blocks extracted for each stroke participant.*



Supplementary Figure 7. *% MRBD plotted during the motor task for the 70 Hz tACS stimulation session during the baseline, 15 min post-stimulation, and 45 min post-stimulation time blocks extracted for each stroke participant.*