Characterization of Beta Bursts in the Motor Cortex and their Association with Motor Performance

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ABSTRACT

Neurorehabilitation has undergone a radical transformation, driven mainly by new technologies such as non-invasive brain stimulation (NIBS) and neuroimaging. As such, magnetoencephalography (MEG) and electroencephalography (EEG) are neuroimaging modalities that can provide rich information about brain function, allowing us to study how it is modulated under different conditions. Using these modalities, it has been shown that movement production leads to a decrease in the average power of the MEG/EEG signal within the beta range (15-29Hz). More recently, it was also revealed that beta oscillations typically occur in the form of transient bursts (beta bursts), which can be characterized in terms of occurrence, amplitude, and duration. There is compelling evidence suggesting that bursts are associated with important aspects of motor performance. However, their relationship with decreased motor performance observed during aging is not well understood currently. In this context, my project aimed to (1) quantify how beta bursts present during hand movement are modulated by aging, (2) investigate the association between burst characteristics and motor performance, and (3) compare the detection performance of two beta burst detection methods (e.g. traditional threshold-based approach & Gaussian Hidden Markov Models (GMM-HMM)). In line with prior literature, we found greater burst amplitude in older adults across all movement intervals. This was consistent across both threshold and HMM methods. Further, we found significant correlations between task accuracy and burst characteristics during movement and post-movement intervals in the younger and older groups. Collectively, our results provide new insights into the effect of aging on transient beta bursts and their relationship with motor performance. This will set the necessary foundation for developing a closed-loop neurofeedback system using a real-time burst detector to normalize brain oscillatory patterns for individuals with motor deficits.

RÉSUMÉ

La neuroréhabilitation a subi une transformation radicale, portée principalement par les nouvelles technologies telles que la stimulation cérébrale non-invasive (NIBS) et la neuroimagerie. La magnétoencéphalographie (MEG) et l'électroencéphalographie (EEG) sont des modalités de neuroimagerie qui peuvent fournir des informations riches sur la fonction cérébrale, nous permettant d'étudier comment elle est modulée durant différentes conditions. En utilisant ces modalités, il a été montré que la production de mouvement entraîne une diminution de la puissance moyenne du signal MEG/EEG dans la bande bêta (15-29Hz). Plus récemment, il a été démontré que les oscillations bêta se produisent généralement sous la forme de salves transitoires (salves bêta) qui peuvent être caractérisées en termes d'occurrence, d'amplitude et de durée. Il existe des évidences qui démontrent que ces rafales sont associées à des aspects importants de la performance motrice. Cependant, leur relation avec la diminution des performances motrices observée au cours du vieillissement n'est actuellement pas bien comprise. Dans ce contexte, mon projet visait à (1) quantifier la façon dont les rafales bêta présentes lors du mouvement de la main sont modulées par le vieillissement, (2) étudier l'association entre les caractéristiques de ces rafales et les performances motrices, et (3) comparer la performance de détection de deux méthodes permettant de quantifier les rafales bêta (approche traditionnelle basée sur le seuil et modèles de Markov cachés gaussiens (GMM-HMM). Conformément à la littérature antérieure, nous avons trouvé une des rafales de plus grande amplitude chez les personnes âgées à travers tous les intervalles du mouvement. Ce résultat était cohérent pour les deux méthodes de seuil et HMM. De plus, nous avons trouvé des corrélations significatives entre la précision des tâches et les caractéristiques de rafale pendant le mouvement et les intervalles post-mouvement chez nos deux groupes. Nos résultats contribuent à une meilleure connaissance de l'effet du vieillissement sur les rafales bêta transitoires et leur relation avec les performances motrices. Cette connaissance est une étape

nécessaire au développement d'un système de neurofeedback en boucle fermée utilisant un détecteur de rafale en temps réel dans le but normaliser les schémas oscillatoires cérébraux chez les individus présentant des déficits moteurs.

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CONTRIBUTION OF AUTHORS

All the work presented in the thesis was authored by myself in collaboration with my supervisor Dr. Marie-Hélène Boudrias. Listed below are the detailed contributions of each member to this thesis:

Rahul Chatterjee performed data and statistical analysis on an existing dataset, created the figures and tables, interpreted the results from the analyses, and wrote and organized the thesis manuscript.

Marie-Hélène Boudrias contributed to the study design, data collection and organizing of the thesis manuscript.

The authors listed below contributed to participant recruitment, study design and data collection: Alba Xifra-Porxas, Guiomar Niso, Sara Larivière, Michalis Kassinopoulos and Georgios Mitsis. Alba Xifra-Porxas also contributed to the preprocessing of the MEG data.

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Introduction & Statement of the Problem

Neuroimaging techniques, such as magnetoencephalography (MEG) and electroencephalography (EEG), are widely used to study electrical activity from different brain areas and how this activity changes under different conditions such as motor performance, aging or disease state. Using these techniques, it has been shown that movement production leads to a decrease in the average power of the MEG/EEG signal within the beta range (15-29Hz). Recent studies have revealed that beta oscillations in the primary motor area (M1) typically exhibit epochs of higher amplitudes known as bursts, which can be characterized in terms of occurrence, amplitude, and duration. Abnormalities in bursts are also well documented in populations with motor and psychiatric disorders. However, their relationship with motor performance in the context of healthy aging is not well understood. In this context, my project aimed to (1) quantify how beta bursts present during hand movement are modulated by aging, (2) investigate the association between burst characteristics and motor performance, and (3) compare the detection performance of two beta burst detection methods (e.g. traditional threshold-based approach & Gaussian Hidden Markov Models (GMM-HMM).

PREFACE

The content of this thesis will include the following chapters:

Chapter 1: This chapter presents an overview of aging in the brain, common neuroimaging techniques and a theoretical understanding of transient bursts in the beta band. It explores a comprehensive review of the current literature on this topic.

Chapter 2: In this chapter, we provide the rationale for the project, the resulting objectives and the hypotheses.

Chapter 3: This chapter describes the methodology for the study.

Chapter 4: Our research findings are presented in this chapter.

Chapter 5: Comprehensive scholarly discussion of all the findings can be found in this chapter.

Chapter 6: Here, we leave the reader with a summary and future applications of our findings.

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CHAPTER 1 - BACKGROUND INFORMATION

1.1 Aging

With the aging population's rapid growth and longer lifespan, which is expected to grow by 68% over the next 20 years, the number of people with motor and cognitive deficits is becoming a serious concern in the healthcare system [1 - 2]. The burden of the aging population on society and public health support is considerable due to increased costs in disability care, emphasizing the significance of finding strategies to help retain their motor and cognitive abilities.

Previous studies reported difficulty coordinating motion, greater movement variability and decreased accuracy in the aging population [3 - 4]. However, this age-related motor deficit is mainly observed during fine movements and complex tasks. For instance, using a grip force modulation task (5–25% of the maximal voluntary contraction (MVC)), Voelcker-Rehage *et al.* showed that older adults performed with less accuracy and more force variability compared to younger subjects [5]. A study by Fling & Seidler *et al.* reported that older adults exhibited higher force variability during a bimanual independent grip task (dominant hand: constant force target level & non-dominant hand: variable target matched; see ***Fig 1***) [6]. Further, older adults showed poorer long-term retention of motor skills due to deficits in memory consolidation during an accuracy-tracking grip task [7]. Mild parkinsonian signs, such as rigidity, bradykinesia, and tremor, are also commonly observed in healthy older adults [8]. Thus, motor ability deterioration associated with aging processes affect daily activities and living quality of elderly individuals.

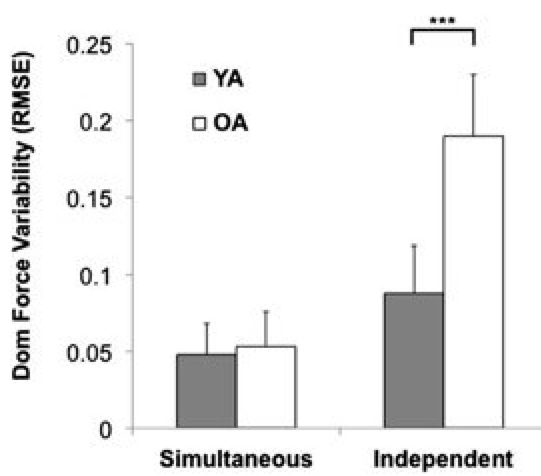

***Fig 1**: Higher dominant hand force variability in older adults [Fling & Seidler. Cerebral Cortex, 2012].*

1.1.1 Age-related structural brain changes

Age-related volume atrophy in different brain regions has been well documented [9 - 14]. However, the rate of volumetric change in different brain areas varies significantly, with certain brain structures showing greater atrophy than others. Initial MRI-based research that explored structural changes in the aging brain revealed that the prefrontal cortex has the greatest volumetric atrophy [9 - 10]. These findings further support the "last in, first out" theory, which claims that the last brain regions to develop are the first to experience age-related atrophy.

More recent studies have confirmed that aging is not limited to the prefrontal region [11 - 14]. For instance, it was shown that aging also impacts the medial temporal lobe structures, areas that are critical for encoding visual information and episodic [12]. Furthermore, volume atrophy was also shown to be present in subcortical regions related to sensorimotor functions, such as the cerebellum and caudate nucleus [13 - 14]. A study by Taubert *et al*. reported a disproportionally steep age-related decline in brain volume and myelin, mainly in the pre-and post-central gyri (see ***Fig 2***), areas playing a crucial role in movement production [11]. Taken together, these findings suggest that brain areas involved in the production of movement are more susceptible to aging than previously thought.

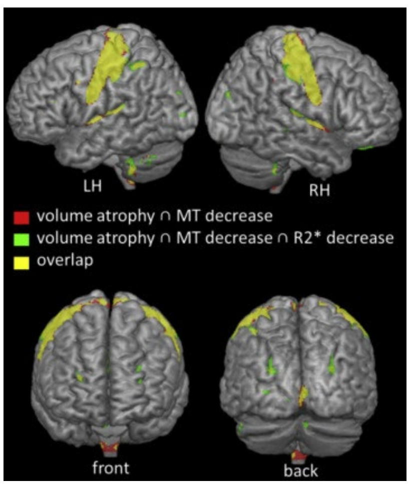

Fig 2*: Age-related differences in motor & sensorimotor areas [Taubert et al. 2020 Neurobio of Aging].*

1.1.2 Aging & decline in motor performance

It is well established that neurodegenerative and neurochemical changes in the brain are associated with a decline in motor performance [6, 15]. For instance, Kennedy *et al*. (2005) reported that the loss of gray matter volume loss in the prefrontal cortex was associated with worst task accuracy during a mirror-tracing task performed with the dominant hand [15]. Furthermore, Fling & Seidler showed that reduced integrity of fiber tracts between motor regions was correlated with a decline in inter-hemispheric inhibition (IHI) and poorer motor performance in older individuals [6].

It is worth mentioning that brain areas affected in healthy aging are also impacted early in neurodegenerative disorders such as Alzheimer's disease (AD) & Parkinson's disease (PD) [8]. Therefore, further research into the effect of structural brain changes on motor functions is necessary to better understand the early signs of neurological disorders (e.g., AD & PD).

1.1.3 Effect of aging on movement production in the motor network

During movement production, there is a neuronal activation or synchronization in different brain areas, including the primary motor cortex (M1), posterior parietal cortex (PPC), the premotor cortex (PC), supplementary motor area (SMA) and subcortical areas, such as the cerebellum and the basal ganglia [16]. It is well established that M1 regulates motor activity by producing movement-specific signals and transmitting them to the muscles via spinal cord circuits and motoneurons. Previous studies also demonstrated that M1 has the highest bilateral activation during movement execution compared to other movement-related brain regions [17 - 18]. M1, in particular, has been shown to have an important function in motor planning and execution [18].

Previous literature has reported the over-activation of brain areas in the aging population as a compensatory mechanism to overcome structural brain changes [19 - 21]. Ward *et al.* [19] found a wider motor network, including the ipsilateral areas to the moving hand, involved during a simple grip task. Over-activation of brain areas has been associated with longer reaction times in older individuals [20]. Further, it is revealed that higher coupling between central, temporal and frontal brain areas leads to a significant delay in movement initiation in older adults [20].

Besides increased recruitment of brain areas, aging also affects the efficiency of information transfer between different functional brain networks. A study by Park *et al*. [21] investigated the efficiency of information transfer in older adults while performing a simple grip task. The authors found a significant decrease in global efficiency, particularly while performing the task with their non-dominant hand. This suggests that the process of information transfer between ipsilateral and contralateral hemispheres is affected in the aging population, and this could negatively influence motor performance in older adults.

1.2 Functional Neuroimaging Modalities

Neuroimaging techniques, such as magnetoencephalography (MEG) and electroencephalography (EEG), are widely used to study electrical activity from different brain areas and how this activity changes under different conditions such as motor performance, aging or disease state.

EEG measures differences in electric potentials on the scalp, while MEG measures brain's magnetic activity. For both modalities, the main generator of electro-magnetic scalp activity is the pyramidal cells in the cortical regions. Although the same neurophysiological processes generate EEG and MEG signals, MEG has the advantage of carrying critical neural information without being distorted by the resistance from the skull and scalp like EEG. Therefore, the MEG signal is less noisy and has a higher temporal resolution than EEG [22 - 23].

Brain signals are categorized into five major frequency bands associated with specific physiological characteristics (see ***Table 1***) [24].

Frequency band	**Frequency**	**Brain states**
Delta (δ)	0.5 – 4 Hz	Stage 3 & stage 4 of the sleep cycle
Theta (θ)	4 – 8 Hz	Deeply relaxed, drowsy, or sleeping states
Alpha (α)	8 – 12 Hz	Very relaxed or motor imagery
Beta (β)	13 – 30 Hz	Attentive, problem-solving, decision making, and focused mental activity especially related to motor or cognitive tasks
Gamma (γ)	30 – 90 Hz	Concentration, memory consolidation & motor learning

Table 1: Physiological significance of different frequency bands in brain signal [24].

In this study, we directed our focus on the beta band because of its well-known connection with motor performance [27, 29].

<u>*Functional Role of Beta Oscillations.*</u> Beta band oscillations in M1 play a significant role in movement execution [25]. During the movement process, the beta power decreases in amplitude, commonly referred to as movement-related beta desynchronization (**MRBD**) [26]. A recent study by Xifra-Porxas *et al.* [27] showed that higher MRBD (i.e. less negative) results in worse motor performance. Another brain oscillatory pattern has also been characterized in the beta band. Following movements, beta rhythms increase in amplitude relative to the resting level, and this is

termed post-movement beta rebound (**PMBR**) [28]. Increased PMBR was shown to correlate with better accuracy during a simple finger-tapping task [29]. These findings suggest that brain oscillation patterns in the beta frequency band are related to various aspects of motor performance.

1.3 Beta Oscillations & Aging

Older adults exhibit higher absolute beta power at rest and during movement execution [27]. Further, it has recently been proposed that absolute beta power must reach a particular threshold level regardless of age to begin a muscle contraction [30]. Therefore, older adults require stronger desynchronization (i.e., larger MRBD) to perform a muscular contraction since they have higher beta power at rest. (see ***Fig 3***) [33 - 35]. Abnormalities in MRBD patterns are also well documented in population with neurological disorders such as stroke [31] and PD [32]. It was also shown that a relative increase in beta power was present in older adults during sustained contractions compared to dynamic contractions [36]. Further, reduced PMBR in elderly individuals was correlated with poor motor performance during stimulus-induced motor tasks [37].

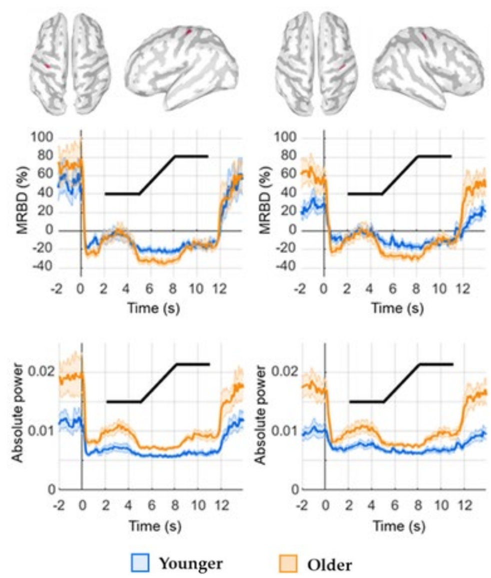

Fig 3: *Greater MRBD & absolute beta power present in older adults (shown in orange) during unimanual task. (A) left M1, (B) right M1. [Xifra-Porxas et al. Neuroimage 2019].*

Collectively, these findings suggest that the age-related changes in beta activity significantly impact motor performance.

1.4 Beta Bursts

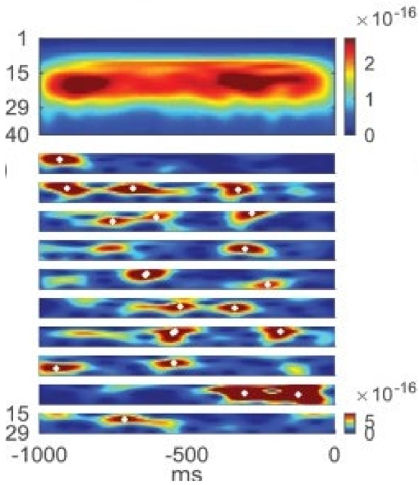

Fig 4: Bursts of beta activity in non-average EEG spectrogram [Shin et al. eLife 2017].

More recent studies have revealed that beta oscillation consists of discrete high amplitude fluctuations or bursts, and these transient events are usually characterized by occurrence, amplitude, and duration (see ***Fig 4***) [38]. The decrease in beta power during movement production (i.e., MRBD) has been associated with transient changes in the probability of occurrence of beta bursts rather than a continuous decrease in MRBD activity [38]. Further, it has been suggested that motor cortical burst activity originated from the alternating dipole current that rises from temporally aligned deep and superficial cortical layers [39]. Abnormalities in bursts are well documented in populations with motor and psychiatric disorders [40, 41]. For instance, a study by Tinkhauser *et al*. [40] reported a higher percentage of longer bursts in PD individuals while in the 'OFF' medication period compared to 'ON' medication. This suggests that greater burst amplitude and longer bursts are associated with poorer motor performance.

1.4.1 Characterization of Beta Bursts

Bursts can be characterized using three primary parameters: rate (the number of bursts within a given period on any given trial), amplitude (maximum of the peak amplitude during the period above threshold), and duration (time over which the amplitude remained above threshold) (see ***Fig 5***). The estimation of these transient events or bursts is typically performed by applying pre-defined thresholds on the amplitude spectrum of the band-pass filtered signal [38 - 41]. There has been a recent trend in analyzing transient events from electrophysiological data using data-driven methods like Hidden Markov models (HMM). The HMM method can identify specific spectral patterns in the MEG time series data by classifying them into pre-defined hidden states (see ***Fig 6***). HMM has been previously used to characterize transient burst states during simple motor tasks to complex motor learning tasks [42, 43] and to estimate functional connectivity between different brain regions during movement execution [43].

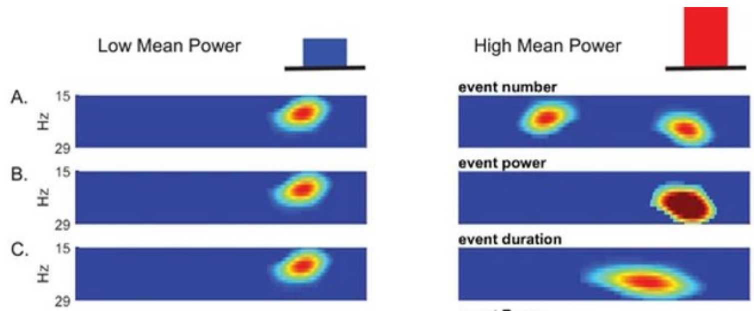

Fig 5*: Burst characteristics (event number, power & duration) in non-average EEG spectrogram [Shin et al. eLife 2017].*

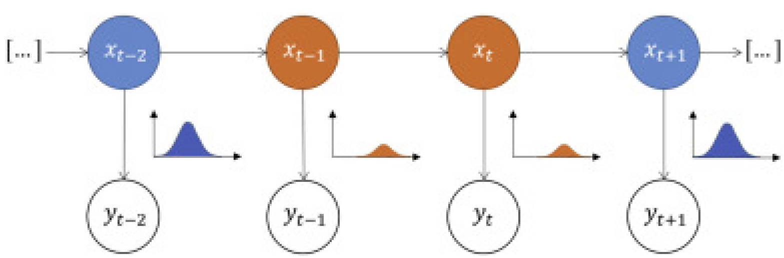

Fig 6*: Schematic diagram of a simple HMM, y_t - MEG time-series data and x_t - an underlying (hidden) state [Seedat et al. 2020].*

HMM can overcome key challenges to burst detection, such as distinguishing between bursts of different frequency bands and detecting bursts without pre-defined thresholds. A recent study by Seedat *et al*. reported that 90% of HMM-identified bursts were detected in comparison to when using the threshold method [43], suggesting that both methods are quite similar in terms of performance for burst identification. No study, however, has systematically compared burst characteristics of both methods in terms of their association with behavioural outcomes or motor performance. Future research on this topic will be critical in determining which method is better in detecting transient events that are more directly related to changes in brain circuitry.

1.4.2 Beta Bursts & Motor Performance

There is converging evidence for an association between cortical beta bursts with movement planning and task accuracy [44, 45]. Pre-movement bursts in M1 have been shown to be related to the degree of motor preparation i.e., increased rate of bursts before movements were linked to longer reaction time (see ***Fig*** *7*). More bursts present during PMBR, in turn, have been associated with better task accuracy [44]. As shown in a recent study [45], visual neurofeedback training can improve response time in healthy participants by suppressing beta bursts before movement initiation. Further, modulation of beta burst characteristics (i.e. burst rate & duration) was shown to enhance motor performance using both conventional and adaptive deep brain stimulation (DBS) [46]. Together, these results indicate that beta bursts are a predominant feature in the motor system.

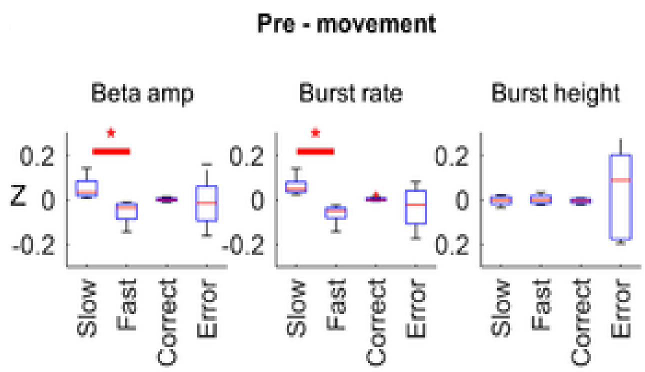

Fig *7: Pre-movement bursts related to motor preparation [Simon et al. Plos Biol 2019].*

1.4.3 Beta Bursts & Aging

A recent MEG study has shown that burst characteristics are affected by aging [47]. Using a unimanual finger-tapping task, prominent age-related changes in burst rate and amplitude during rest, pre-and post-movement intervals were identified (see ***Fig 8***). During pre-movement intervals, there was an increase in both burst rate and amplitude associated with age. This was thought to be the main source of the increased average baseline spectral power observed in older subjects. However, no association was reported between age and other burst characteristics during the movement period. This was believed to be due to higher variance and reduced occurrence of bursts during movement compared to the other intervals. The association between age-related changes in burst characteristics and motor performance is still unknown. Further, burst characteristics during unimanual and bimanual grip tasks are yet to be investigated in the context of healthy aging.

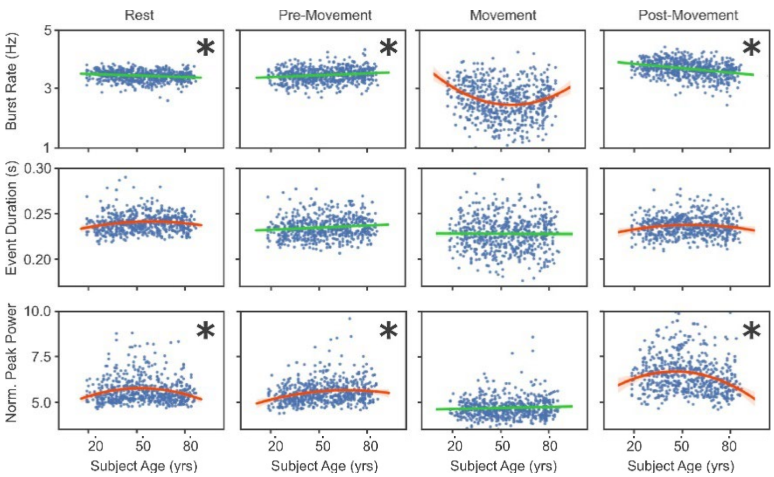

Fig 8*: Age-related changes in burst characteristics [Brady et al. 2020].*

CHAPTER 2 - OBJECTIVES & HYPOTHESES

Objectives

It is well established that beta oscillation patterns and burst characteristics are affected by aging during movement tasks. However, not much is known in terms of how age-related changes in burst characteristics can impact on brain-behavior interactions. In this context, the **objectives** of this study were to:

1. estimate the age-related changes in beta burst characteristics (e.g. rate, amplitude & duration) during unimanual and bimanual grip tasks;
2. quantify the relationship between burst characteristics and motor performance; and
3. compare the performance of the two detection methods, e.g. traditional threshold-based approach and Gaussian HMM, in detecting age-related trends in burst characteristics.

Hypotheses

Objective 1. Based on previous findings, older adults exhibit higher absolute beta power at rest and during movement production. Since the occurrence of beta bursts is highly correlated with trial-averaged beta power, we hypothesized that a higher β-burst rate and amplitude will be more present in older subjects than in their younger counterparts.

A relative increase in the beta power is known to be present during steady muscle contractions compared to dynamic ones. We hypothesized that sustained contractions will be associated with lower burst rates (i.e. movement intervals with constant target-force level) when compared to dynamic ones (i.e. movement intervals with varying target-force level) during the unimanual task.

Objective 2. Previous studies showed that greater MRBD (i.e. more negative) during a bimanual grip task is associated with poorer task performance [27]. Therefore, we hypothesized that lower burst-amplitude during the bimanual task will be correlated with better task accuracy.

Objective 3. Previous studies have reported a high degree of overlap between HMM and threshold method bursts [43]. Accordingly, we expected to find consistent age-related rends in burst characteristics across both methods. However, the studies that investigated the relationship between burst characteristics and motor performance only used the threshold approach. There is no prior evidence of a connection between HMM-identified bursts and motor performance. Furthermore, one of the fundamental assumptions of the HMM method is that hidden states are mutually exclusive, which implies that HMM method can not handle the co-occurrence of multiple brain states [42, 43]. Therefore, HMM may be incapable of capturing accurate physiological representations of brain activity related to complex tasks that engage several brain areas in both hemispheres (e.g. a bimanual or dynamic grip task). We further hypothesized that the threshold method bursts would outperform HMM in predicting motor performance.

CHAPTER 3 - METHODOLOGY

3.1 Dataset

The study used previously collected MEG data from younger and older adults acquired at rest and during handgrip paradigms, including unimanual and bimanual tasks [27].

Study Participants. In this study, a total of 12 younger and 12 older healthy individuals were recruited. Participants' demographic information included their age, handedness, and medical history were collected. The Nine Hole Peg Test (9HPT), Box and Blocks Test (BBT), Purdue Pegboard Test (PPT), and Hand Grip Strength (HGS) were used to assess motor abilities in both hands [49 - 52]. This was done to define a broad variety of upper limb motor capabilities, ranging from manual dexterity to strength. The Mini-Mental State Examination (MMSE, (Folstein et al., 1975)) was also used to assess participants for cognitive state. The inclusion and exclusion criteria for participation were as follows:

Inclusion criteria

- ❑ Healthy male or female between the age of 18 and 30 years old were included in the younger group.
- ❑ Healthy male or female between the age of 60 and 74 years old were included in the older group.
- ❑ Right-hand dominance was assessed using The Edinburgh Handedness Inventory [48].

Exclusion Criteria

- ❑ Subjects with psychiatric disease or cognitive impairment or self-reported history of major or unstable medical illness, significant neurological history (e.g. epilepsy, brain tumor, stroke).

- ❏ Subjects with history of head trauma with loss of consciousness for greater than 5 min, as well as individuals taking psychotropic medications.
- ❏ Participants with metal artifacts i.e. presence of ferromagnetic material (e.g. dental braces, metal implants and/or crowns).

<u>Sample size and how it was determined</u>

Previous published studies investigating the effects of aging on beta oscillation have shown changes in brain networks and behavior using a similar sample size. Based on these studies, the same number of participants were recruited (Schmiedt-Fehr *et al*. 2016, Heinrichs-Graham and Wilson *et al*. 2016).

<u>Experiment paradigm</u>

Behavioral assessment tests

At the beginning of the experimental session, participants completed four behavioral assessment tests for evaluating hand function. The scores of the BBT, 9HPT and PPT were further used to evaluate correlation with Rest burst characteristics.

1) Box and Blocks Test (BBT) - The BBT [49] was used to assess manual dexterity by counting the number of blocks transported from one compartment of a box to another of equal size within 1 min.
2) Nine Hole Peg Test (9HPT) - The 9HPT [50] was measured in seconds, showing how fast each participant placed and removed nine pegs into the holes.

3) Purdue Pegboard Test (PPT) - The PPT [51] was measured by the number of pins placed into holes within 30 s (using dominant, non-dominant and both hands) or the total number of pins, collars and washers assembled within 60 s (assembly test with both hands).

4) Hand Grip Strength (HGS) - The HGS [52] was performed using both hands and it was measured in kilograms.

Description of methodology

A flowchart of the protocol can be found in **Fig 9**. Prior to the acquisition of each session, empty room noise data was collected to get an insight into the environmental noise conditions. The protocol consisted of a unimanual and a bimanual grip task, alternated by three resting-state periods. For the unimanual task, participants had to track a ramp target ranging from 15% to 30% of their MVC. Participants had to exert a constant force at 15% of their MVC using both hands for the bimanual task. The MVC of each participant was measured after the first resting-state period.

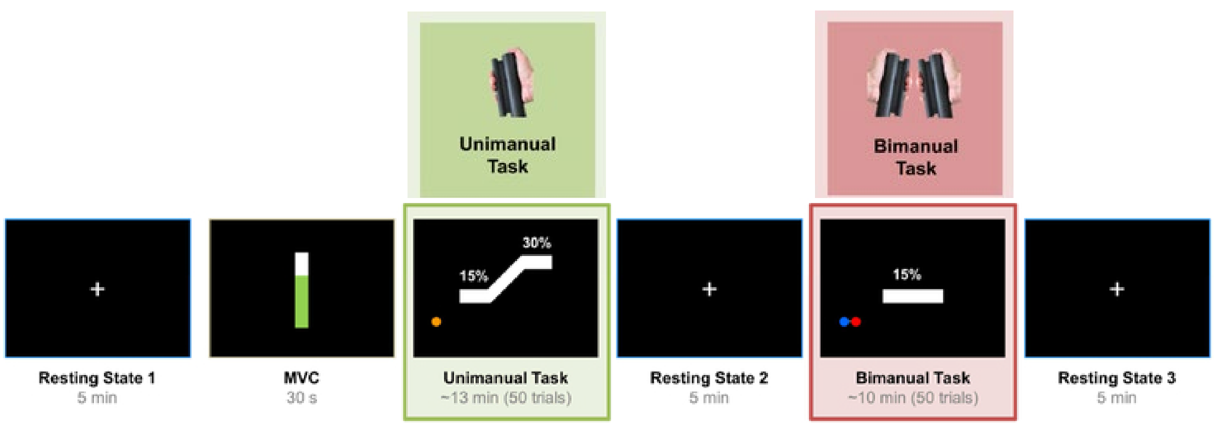

Fig 9: Schematic overview of the protocol (Xifra-Porxas et al. Neuroimage 2019).

Measurements & study instruments

Grip force measurement. A pair of non-magnetic, non-electronic hand grippers (Current Designs Inc, USA) was used to measure the grip force of the participants while conducting the motor tasks.

Neuroimaging data acquisition. MEG data were recorded using a 275-channel CTF whole-head system at the McConnell Brain Imaging Centre (BIC) of the Montreal Neurological Institute (MNI).

Other measurements. A Polhemus Fastrak device was used to compute the 3D digitization of the head shape using uniformly distributed ~ 100 head points. Individual T1-weighted MRI images were acquired on a 3T MRI scanner (Siemens Prisma). The position of the head localization coils (nasion, left and right pre-auricular) and the head-surface points were later used to obtain co-registration between the MEG and MRI coordinate systems.

Task accuracy. This was measured as the root mean squared error between the target force level and the subject's applied force at a given time. For the unimanual task, task accuracy was computed separately for each of the three movement intervals (M1, M2 & M3, see section **3.2** below). For the bimanual task, it was measured during the 6 sec movement period of each trial.

3.2 Data Preprocessing

Noise removal. Raw MEG data were filtered (1 to 150 Hz bandpass) and power line artifacts around 60 Hz were removed using notch filters. Electrocardiogram (ECG) and electrooculography (EOG) signals were used to identify the cardiac and eye-movement artifacts and these artifacts were corrected using signal-space projection (SSP). Further, independent component analysis

(A) **(B)**

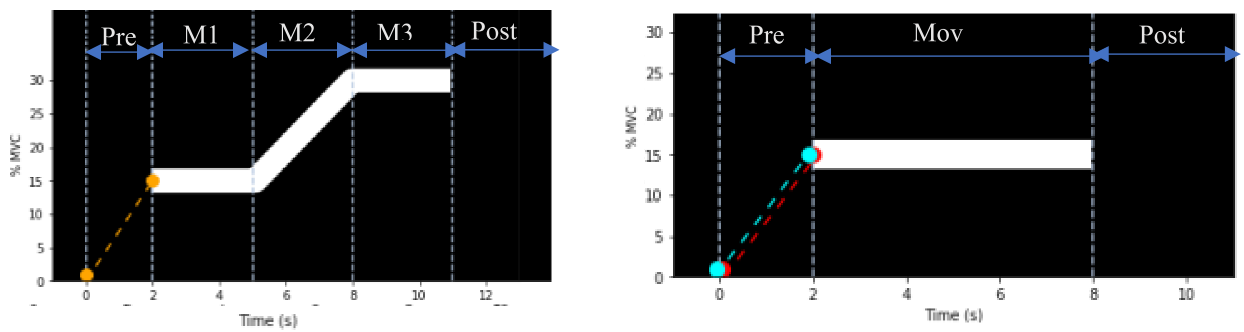

Fig 10: *Task intervals: A) Unimanual task.* ***Pre, M1, M2, M3, Post*** *(B) Bimanual task-* ***Pre, Mov, Post.***

(ICA) was applied to remove artifacts related to external magnetic fields. Noisy channels or epochs presented motion artifacts (i.e. segments where subjects moved more than 5 mm between head position measurements) were removed. Further, MEG data from the unimanual task were segmented into 16.5 s epochs extending from 2.5 s before and 14 s after the visual cue, and data from the bimanual task were epoched from 2.5 s before and 11 s after the visual cue and the 5-min resting-state recordings were segmented in epochs of 5 s.

<u>*Task Intervals.*</u> The data were divided into 5 intervals for the unimanual task (see ***Fig 10*** (**A**)): Movement preparation (**Pre**), Movement – 15% MVC (**M1**), Movement – 15 to 30% MVC (**M2**), Movement – 30% MVC (**M3**), and Post-movement (**Post**). The data were divided into 3 intervals for the bimanual task (see ***Fig 10*** (**B**)): Movement preparation (**Pre**), Movement – 15% MVC (**Mov**), and Post-movement (**Post**). The 5-min recorded before the unimanual task while the subjects rested was used for the **Rest** interval.

3.3 Time Frequency map (Morlet wavelet)

<u>*MEG β power & β bursts.*</u> In this study, we focused on M1, as it is well established that M1 plays an active role during movement execution and is also affected by aging processes. Therefore, signals from the targeted sensors located above M1 in the left (MLC 17) and right (MRC 17) hemispheres (see ***Fig 11***) were extracted for subsequent analyses. Single-trial MEG waveforms were extracted per subject and decomposed to the time-frequency (TF) domain using Morlet wavelets (time resolution=3 s, central frequency=1 Hz) in the following frequency band: beta (15 – 29 Hz). The evoked response was removed from each trial before computing the TF decomposition [53].

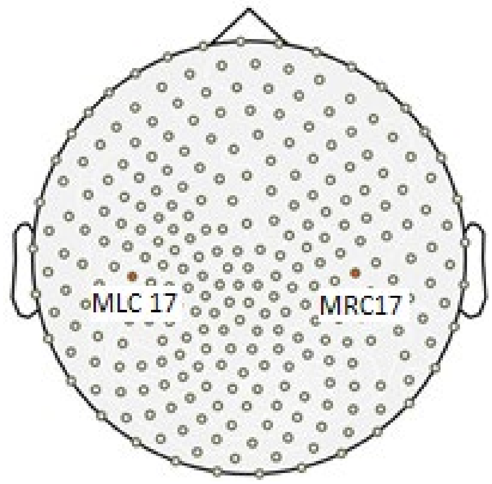

Fig 11: *MEG sensor locations (MLC 17 & MRC 17).*

3.4 Beta burst detection

<u>*Threshold method.*</u> We applied a threshold corresponding to the power of the signal followed by a second threshold reflecting the duration of the fluctuations or bursts. We used the 75th percentile value of the absolute beta power [38 - 41] and we set the minimum burst duration as

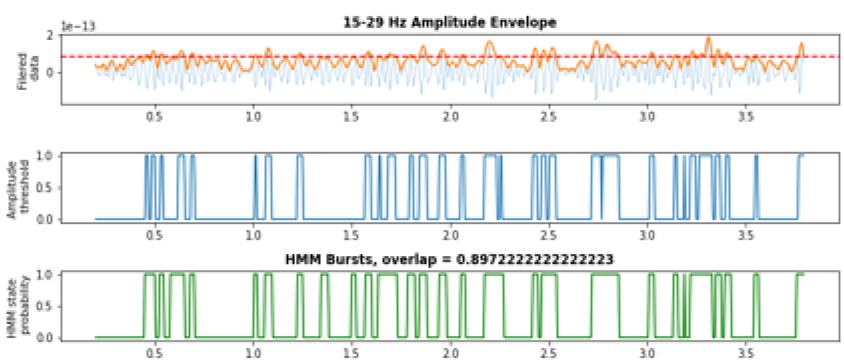

Fig 12: *Detection of beta 'bursts' in a single trial data using threshold & HMM method.*

100 ms to account for rapid fluctuations that may result in false bursts (see ***Fig 12***) [40, 46]. Further, we used different thresholds for different intervals (i.e., Rest, Pre, Mov, M1, M2, M3 & Post) (see ***Fig 10***).

Beta burst characteristics were computed as follows: **rate** as the number of bursts within a given period (1 sec) on any given trial, **amplitude** as the maximum of the peak amplitude during the period above threshold**,** and **duration** as the time over which the amplitude remained above threshold.

<u>*HMM method.*</u> We used HMM with a Gaussian observation model (see ***Fig 13***) on the amplitude envelope beta time-courses [42]. In this method, two states were characterised: high amplitude fluctuations **('Burst'** states) and low amplitude state. The occurrence of a burst event was defined by a specific occurrence of the burst state. For the HMM method, burst characteristics were defined as follows: **rate** as the number of visits to the burst state normalised by time (1 Sec), **amplitude as** the maximum value of the beta envelope during each occurrence of the burst state, **duration** as the time spent in the burst state.

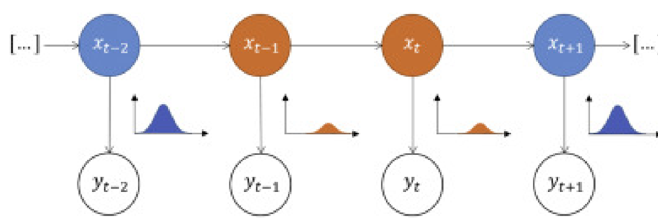

***Fig 13**: Schematic of HMM. At each time t, y_t refers to MEG data and x_t refers to corresponding hidden states [Zelekha A. et al. Neuroimage 2020].*

We decided to focus on the findings of the threshold method because most of prior literature used this technique to detect transient bursts from EEG/MEG signals [38 - 41] (see sections **4.1**, **4.2**, **4.3**). Further, we presented a comparative analysis of the results of the two methods (see section **4.4**).

3.5 Statistical Analyses

Linear mixed-effect models (LMMs) with experimental trial intervals (i.e. Rest, Pre, M1, M2, M3 & Post for the unimanual & Rest, Pre, Mov & Post for the bimanual task) and age group as 'fixed effect' factors were used to compare burst characteristics between groups and intervals. For each of the burst characteristics, we performed LMM analysis using the following formulas:

Rate ~ Group + Interval + Group * Interval
Bamp ~ Group + Interval + Group * Interval
Duration ~ Group + Interval + Group * Interval

Here, burst characteristics (Rate, Bamp & Duration) are 'response variables', and the model terms to the right of the tilde character ("~"), denote 'fixed effects' and the interaction ('*') between fixed effects. We performed the above analyses separately for the unimanual and bimanual tasks. Post-hoc analyses were performed to get contrasts for within and between-subject comparisons, and *p*-values were obtained using the Satterthwaite approximation. Bonferroni correction was applied to adjust for multiple comparisons. The *p*-values less than 0.05 were considered significant. All statistical analysis was performed in the software R-Studio using the following packages: 'lmer', 'lmerTest' and 'emmeans'.

3.6 Correlation between bursts & motor performance

We performed linear regression analysis between the response variable (i.e. behavioural assessment score (behavioural scores of the PPT, NHPT & BBT & task accuracy) and the predictor variable (i.e. group of participants). If significant differences between age groups were found, we performed the subsequent analyses separately for the two groups. When no difference was found between the groups, the data were combined for further analyses.

A multiple linear regression model was then used to evaluate the relationship between the response variable (i.e. behavioural scores & task accuracy) and predictor variables (i.e. burst characteristics - rate, amplitude & duration).

3.7 Burst overlap analysis between HMM & threshold method

The percentage of overlap between HMM and threshold method bursts were computed using the following the formula:

Percentage over lap = (Σ T1 .* T2) * 100/n;
n = no of time points in a single trial,
T1 = HMM burst time course
T2 = threshold burst time course

Finally, we averaged the percentage overlap across all intervals (Rest, Pre, Mov & Post) and groups (i.e. young & old) and motor paradigms (i.e. unimanual & bimanual).

3.8 Overall presentation of the analyses

A) LMM

We used LMM for the following analyses. Analysis-I: Comparison between groups & between intervals for the unimanual task (**Section – 4.1.1**). Analysis-II: Comparison between groups &

between intervals for the bimanual task (left M1) (**Section – 4.1.2**). Analysis-III: Comparison between groups & between intervals for the unimanual task (right M1) (**Section – 4.1.2**).

B) Regression analysis (Unimanual task)

For the unimanual task, regression analyses were separately done for the following 5 intervals: Analysis-I: between task accuracy (intervals M1, M2 & M3) & burst characteristics (something is missing here) (**Section – 4.2.1**). Analysis-II: between task accuracy (average of intervals M1, M2, M3) & burst characteristics (Post) (**Section – 4.2.1**). Analysis-III: between task accuracy (average of intervals M1, M2, M3) & burst characteristics (Pre) (**Section – 4.2.1**).

C) Regression analysis (Bimanual task)

For the bimanual task, regression analyses were separately done for the following 5 intervals: Analysis-I: between task accuracy (Mov) & burst characteristics (Mov) (**Section – 4.2.2**). Analysis-II: between task accuracy (Mov) & burst characteristics (Post) (**Section – 4.2.2**). Analysis-III: between task accuracy (Mov) & burst characteristics (Pre) (**Section – 4.2.2**).

D) Regression analysis (Behavioural assessment)

For behavioral assessment, regression analyses were separately done for the following 5 intervals: Analysis-I: between motor score (PPT) & burst characteristics (Rest) (**Section – 4.2.3.1**). Analysis-II: between motor score (NHPT) & burst characteristics (Rest) (**Section – 4.3.3.2**). Analysis-III: between motor score (BBT) & burst characteristics (Rest) (**Section – 4.3.3.3**).

Due to the limited number of participants, all the above-mentioned statistical analyses were performed on single-trial MEG data, not trial-averaged values. Therefore, for each subject, we ended up having 50 samples (i.e. no of trials), and on a group level, we had 600 samples (50 * n, n = 12 subjects).

CHAPTER 4 - RESULT

4.1 Burst characteristics between groups & intervals using the threshold method

4.1.1 Unimanual task

4.1.1.1 Comparison between groups

Burst rate. The LMM revealed a significant group effect (*Bonferroni adjusted p* < 0.003, F = 1.88) . Post-hoc tests did not show any significant difference between younger and older adults across any of the task intervals (see ***Fig 14***).

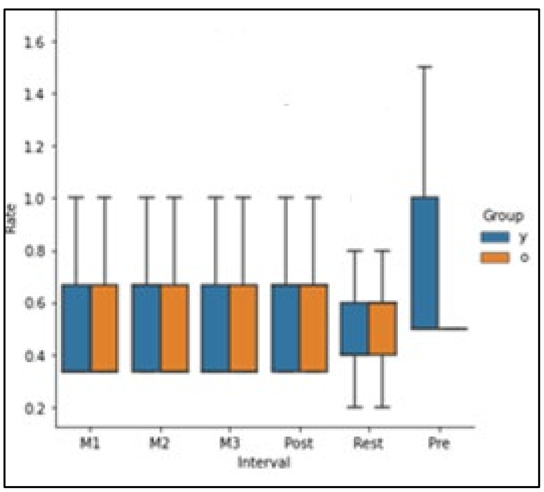

Fig 14*: Burst rate (young vs. old) across different intervals (Rest, Pre, M1, M2, M3 & Post). Rate is expressed in terms of event/sec.*

<u>Burst amplitude (bamp).</u> A significant difference was found between the younger and older groups (LMM Group effect: *Bonferroni adjusted* $p < 0.001$, F value = 243.54). Further, Post-hoc tests revealed that older adults had a significantly (*Bonferroni adjusted* $p < 0.001$) higher burst amplitude than younger subjects across all intervals (Rest, Pre, M1, M2, M3 & Post) (see ***Fig 15***).

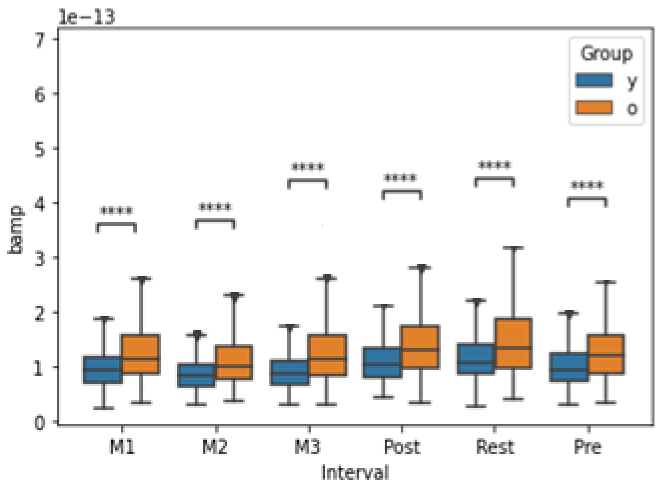

Fig 15: *Burst amplitude (young vs. old) across different intervals (Rest, Pre, M1, M2, M3 & Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences marked by (*).

<u>Burst duration.</u> LMM model revealed no significant group effect (*Bonferroni adjusted* $p < 0.3$, F value = 0.82).

4.1.1.2 Comparison between intervals

<u>Burst rate.</u> Significant difference in burst rate between intervals (LMM Interval effect: *Bonferroni adjusted p* < 0.001, F value = 5.33) was found. However, no significant group-interval interaction was observed (LMM Group*Interval effect: *Bonferroni adjusted p* < 0.9). Further, post-hoc analysis of data from younger and older subjects lumped together revealed that burst rate at Rest was significantly lower compared to the movement (M1, M2 & M3) and Post intervals (see ***Fig 16*** & in ***Table 2*** Appendix).

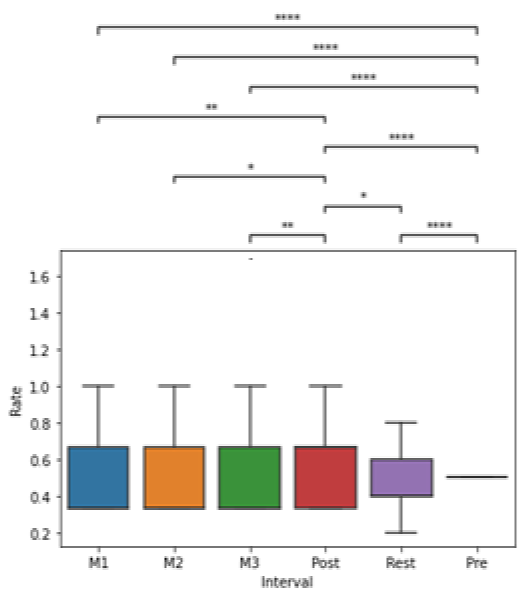

Fig 16: *Burst rate between different intervals (Rest, Pre, M1, M2, M3 & Post). Rate is expressed in terms of event/sec.*

Significant differences marked by (*).

Burst amplitude. Significant difference in burst amplitude was found between task intervals (LMM interval effect: *Bonferroni adjusted p* < 0.001, F value = 32.71). However, the LMM revealed no significant interaction between group and intervals (Group*Interval effect: *Bonferroni adjusted p* < 0.23) (see in ***Table 3*** Appendix). Further, post-hoc tests on data of the two groups lumped together showed that burst amplitude during the Pre and movement intervals (M1, M2 & M3) were significantly less than the Post and Rest periods (see ***Fig 17).***

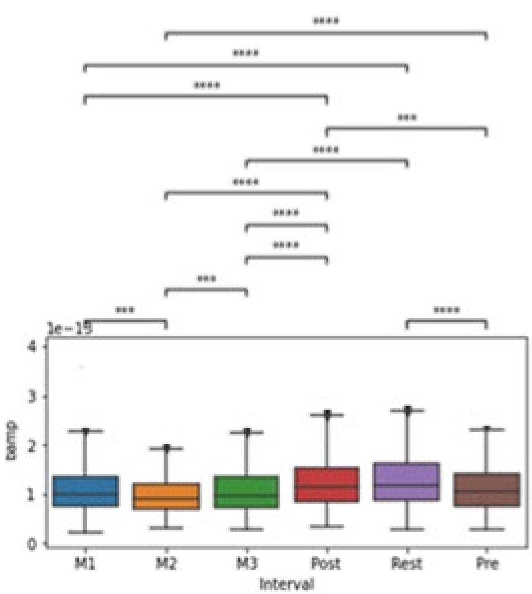

Fig 17: *Burst amplitude between different intervals (Rest, Pre, M1, M2, M3 & Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences marked by (*).

<u>Burst duration.</u> The LMM revealed significant effect in burst duration between intervals (LMM Interval effect: *Bonferroni adjusted* $p < 0.001$, $F = 3.34$). However, no group - interval interaction was found (Group*Interval effect: *Bonferroni adjusted* $p < 0.9$). Further post-hoc tests on data from all subjects lumped together (see ***Table 4*** in Appendix) indicated that burst duration during Pre was significantly shorter than for the movement (M1, M2 & M3), Post and Rest intervals (see ***Fig 18***)

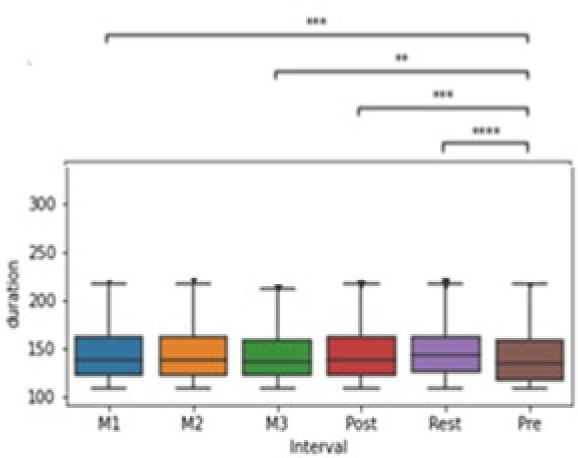

Fig 18*: Burst duration between different intervals (Rest, Pre, M1, M2, M3 & Post). Duration is expressed in terms ms.*

Significant differences marked by (*).

4.1.2 Bimanual task

Between-group (young vs. old) and between-interval (young & old) comparisons of burst characteristics (left & right M1) are presented below.

4.1.2.1 Comparison between groups (young vs. old)

4.1.2.1.1 Left M1

<u>*Burst rate.*</u>

The LMM revealed a significant group effect (*Bonferroni adjusted p* < 0.009, F value = 6.81). Post-hoc tests did not show any significant difference between younger and older adults across any of the task intervals (see ***Fig 19***).

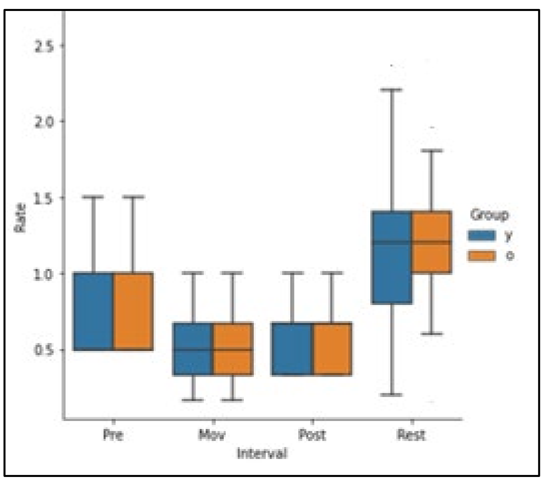

Fig 19: *Burst rate (young vs. old) across different intervals (Rest, Pre, Mov & Post). Rate are expressed in terms of event/sec.*

Burst amplitude (bamp).

Significant group effect (*Bonferroni adjusted p* < 0.001, F value = 153.44) in burst amplitude was found. Further post-hoc tests revealed that older adults have a significantly (*Bonferroni adjusted p* < 0.001) higher burst amplitude than younger subjects across all intervals (see ***Fig 20***).

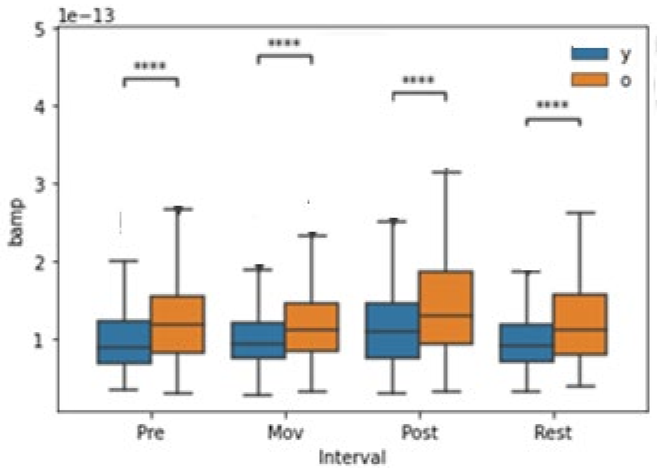

Fig 20*: Burst amplitude (young vs. old) across different intervals (Rest, Pre, Mov, Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences are marked by (*).

Burst duration. LMM model revealed no significant group effect (*Bonferroni adjusted p* < 0.08, F value = 3.02).

4.1.2.1.2 Right M1

Burst rate. The LMM revealed no significant group effect (*Bonferroni adjusted p* < 0.9) in burst rate.

Burst amplitude. Significant difference in burst amplitude between younger and older groups (LMM Group effect: *Bonferroni adjusted p* < 0.001, F value = 283.54) was found. Further, post-hoc tests revealed that older adults had a significantly (*Bonferroni adjusted p* < 0.001) higher burst amplitude than younger subjects across all intervals (Mov, Post, Rest & Pre) (see ***Fig 21***).

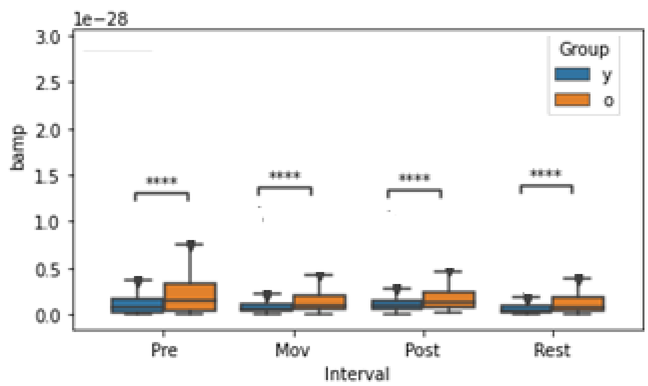

Fig 21*: Burst amplitude (young vs. old) across different intervals (Rest, Pre, Mov & Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences are marked by (*).

Burst duration. LMM model revealed no significant group effect (*Bonferroni adjusted p* < 0.9, F = 0.82).

4.1.2.2 Comparison between intervals

4.1.2.2.1 Left M1

Burst rate. Significant difference in burst rate between intervals (LMM Interval effect: *Bonferroni adjusted p* < 0.001, F = 1339.19) was found. However, LMM revealed no significant interaction between groups and intervals (LMM Group*Interval effect: *Bonferroni adjusted p* < 0.8) Further post-hoc tests of all data grouped together (see ***Table 5*** in appendix) showed that burst rate during Rest were significantly higher than the Mov, Pre and Post intervals (see ***Fig 22***).

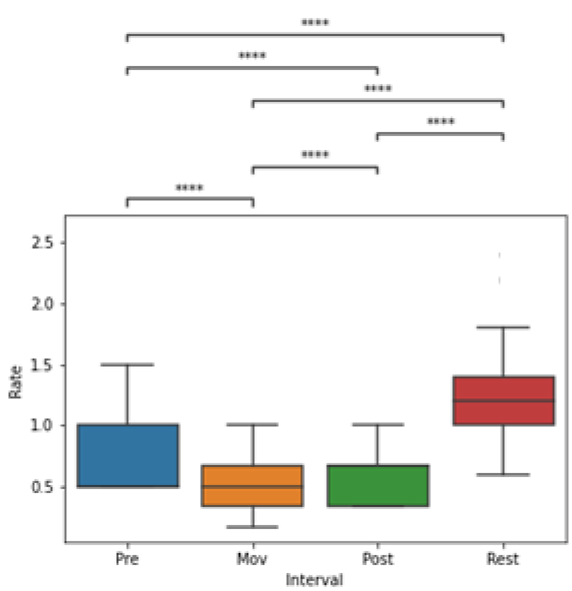

Fig 22: *Burst rate between different intervals (Rest, Pre, Mov, Post). Rate is expressed in terms of event/sec.*

Significant differences marked by (*).

Burst amplitude. Significant difference in burst amplitude between task intervals (LMM interval effect: *Bonferroni adjusted p* < 0.001, F = 79.33) was found. However, the LMM revealed no significant interaction between groups and intervals (Group*Interval effect: *Bonferroni adjusted p* < 0.23). Further, post-hoc tests of data from all subjects lumped together showed that burst amplitude in Post was significantly higher than the Rest, Pre and Mov intervals (see ***Fig 23, Table 6*** in appendix).

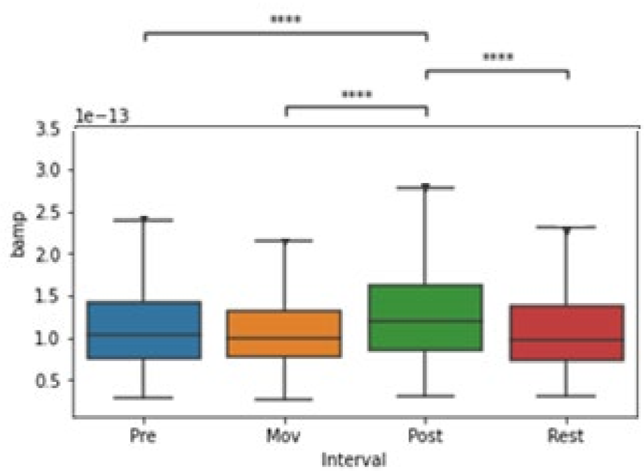

Fig 23*: Burst amplitude between different intervals (Rest, Pre, Mov & Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences marked by (*).

<u>Burst duration.</u> Significant difference in burst duration between intervals (LMM Interval effect: *Bonferroni adjusted p* < 0.001, F = 511.41) was found. However, no group - interval interaction was found (Group*Interval effect: *Bonferroni adjusted p* < 0.9). Further post-hoc tests of all data grouped together (see ***Table** 7*) revealed that burst duration during Rest was significantly longer than all other intervals (see ***Fig 24).*** Further we found burst duration during Mov interval to be significantly longer than Post and Pre intervals (see ***Fig 24)***.

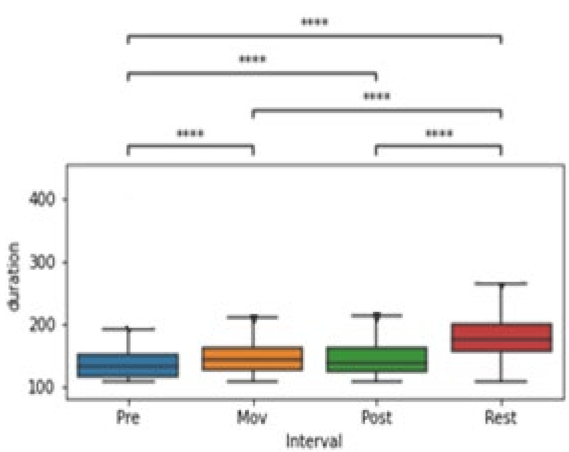

***Fig 24**: Burst duration between different intervals (Rest, Pre, Mov & Post). Duration is expressed in terms ms.*

Significant differences marked by (*).

4.1.2.2.2 Right M1

<u>*Burst rate.*</u> Significant difference in burst rate between task intervals (LMM interval effect: *Bonferroni adjusted p* < 0.001, F = 939.19) was found. However, the LMM revealed no significant interaction between groups and intervals (Group*Interval effect: *Bonferroni adjusted p* < 0.6). Further post-hoc tests of data from all subjects lumped together (see ***Table 8Table 8*** in Appendix) shows that burst rate during Mov was significantly lower (Bonferroni adjusted p < 0.001) than Pre, Rest and Post intervals (see ***Fig 25***). Further, we found that burst rate during Pre and Post intervals were significantly higher (*Bonferroni adjusted p* < 0.001) than Rest.

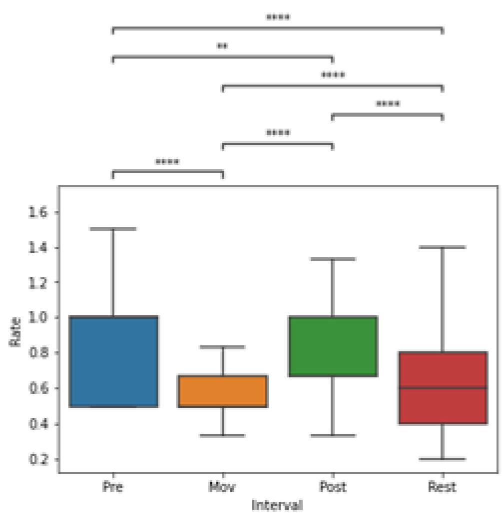

Fig 25*: Burst rate between different intervals (Rest, Pre, Mov & Post). Rate is expressed in terms of event/sec.*

Significant differences marked by (*).

<u>Burst amplitude (bamp).</u> LMM revealed significant difference in burst amplitude between intervals (LMM Interval effect: *Bonferroni adjusted p* < 0.001, F value = 35.4). However, no group - interval interaction was found (LMM Group*Interval effect: *Bonferroni adjusted p* < 0.7). Further, post-hoc tests of data from all subjects grouped together (see ***Table 9*** in Appendix) showed that burst amplitude during the Pre interval was significantly higher than the Mov, Post and Rest intervals. Also, burst amplitude during Post was significantly higher than the Mov and the Rest intervals (see ***Fig 26***).

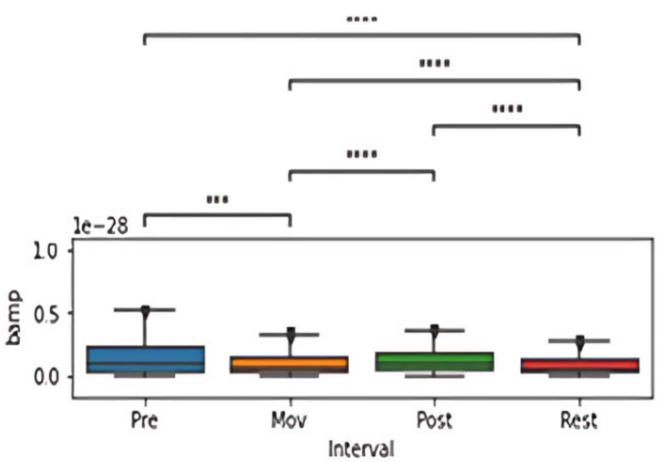

Fig 26: *Burst amplitude between different intervals (Rest, Pre, Mov & Post). Amplitude (bamp) is expressed in terms of peak beta amplitude over threshold (µV).*

Significant differences marked by (*).

<u>*Burst duration.*</u> Significant difference in burst duration between intervals (LMM Interval effect: *Bonferroni adjusted p* < 0.001) was found. However, the LMM revealed no significant interaction between groups and intervals (LMM Group*Interval effect: *Bonferroni adjusted p* < 0.9). Further, post-hoc tests of data from younger and older subjects lumped together (see ***Table 10***) showed that burst duration in movement intervals were significantly (*Bonferroni adjusted p* < 0.001) longer than all other intervals including Rest, Post and Mov (see ***Fig** 27)*. Further we found burst duration during Rest to be significantly (*Bonferroni adjusted p* < 0.01) shorter than Post and Mov intervals.

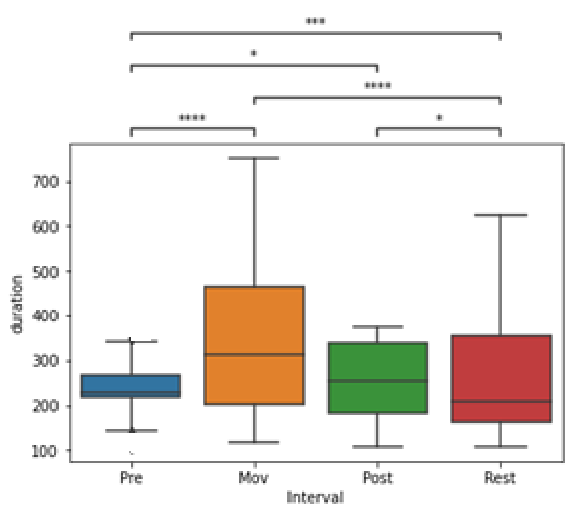

***Fig 27**: Burst duration between different intervals (Rest, Pre, Mov & Post). Duration is expressed in terms ms.*

Significant differences marked by (*).

4.2 Relationship between Burst Characteristics & Motor Performance using the Threshold Method

4.2.1 Unimanual Task

4.2.1.1 Movement Interval (M1). No significant (*Bonferroni adjusted p* < 0.9) group effect was found in task accuracy during M1 (see ***Fig 10***). Data from younger and older subjects were combined for the subsequent regression analyses. We found a significant (*Bonferroni adjusted p* < 0.01) but weak correlation (Adjusted R-squared: 0.01) between task accuracy and the aggregate of all burst characteristics (rate, amplitude & duration). Further, linear regression using individual burst characteristics revealed that only rate was significantly (*Bonferroni adjusted p* $<$ 0.009) correlated with the task accuracy, but the correlation (Adjusted R-squared: 0.00804) was very weak compared to when all burst characteristics were combined (see ***Fig 28***).

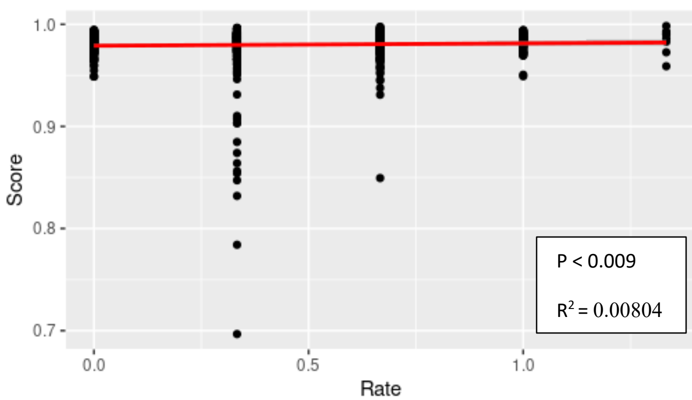

Fig 28: *Positive correlation between burst rate and motor performance (i.e. higher burst rate related to better task accuracy).*

Score refers to task accuracy during M1 interval of individual trials & Rate refers to burst rate (events/sec) during M1 interval of individual trials.

4.2.1.2 Movement Interval (M2). Multiple regression analysis revealed a significant group effect in task accuracy (*Bonferroni adjusted p* < 0.001) during M2. Therefore, subsequent analyses were performed separately on younger and older subjects. No significant correlation between task accuracy and burst characteristics was found for either the younger (*Bonferroni adjusted p* < 0.9) or the older group (*Bonferroni adjusted p* < 0.8).

4.2.1.3 Movement Interval (M3). No significant (*Bonferroni adjusted p* < 0.1) group effect was found in task accuracy during M3. Multiple linear regression analysis revealed no significant (*Bonferroni adjusted p* < 0.2) correlation between task accuracy and all burst characteristics. However, among individual burst characteristics, there was a significant (*Bonferroni adjusted p* < 0.03) but very week correlation (Adjusted R-squared: 0.00234) between burst amplitude and task accuracy (see ***Fig 29***).

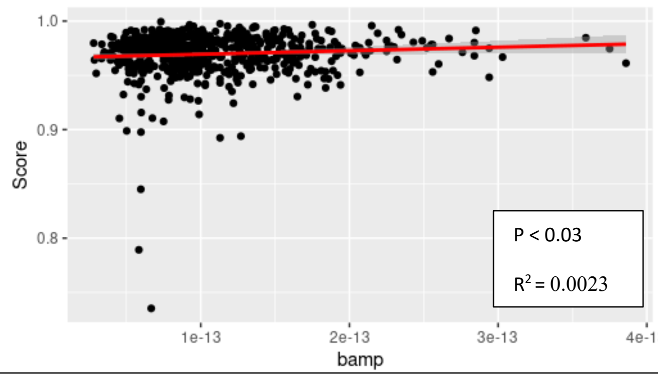

Fig 29: *Positive correlation between burst amplitude (bamp) and motor performance (i.e. higher burst amplitude related to better task accuracy)*

Score refers to task accuracy during M3 interval of individual trials & bamp refers to burst amplitude during M3 interval of individual trials.

4.2.1.4 Preparation Interval (Pre). Multiple regression analysis revealed no significant (*Bonferroni adjusted p* < 0.7) correlation between the task accuracy (averaged across M1, M2 & M3 intervals) and burst characteristics of the Pre interval.

4.2.1.5 Post-movement Interval (Post). No significant (*Bonferroni adjusted p* < 0.6) correlation between the task accuracy (averaged across M1, M2 & M3 intervals) and burst characteristics of Post interval was observed.

4.2.2 Bimanual Task

Results are presented as follow: correlation between task accuracy of the right hand and burst characteristics of left motor area (section **4.3.2.1**) and between task accuracy of the left hand and burst characteristics of the right motor area (section **4.3.2.2**).

4.3.2.1 Left Motor Area

4.3.2.1.1 Movement Interval (Mov)

Multiple regression analysis revealed a significant group effect on task accuracy (*Bonferroni adjusted p* < 0.001) during Mov interval. Therefore, subsequent analyses were performed separately on younger and older subjects.

<u>*Younger Group.*</u>

No significant (*Bonferroni adjusted p* < 0.15) correlation between the task accuracy and all burst characteristics was found. However, among individual burst characteristics, regression analysis revealed a significant (*Bonferroni adjusted p* < 0.02) but very week correlation (Adjusted R-squared: 0.007) between burst rate and task accuracy (see ***Fig 30*).**

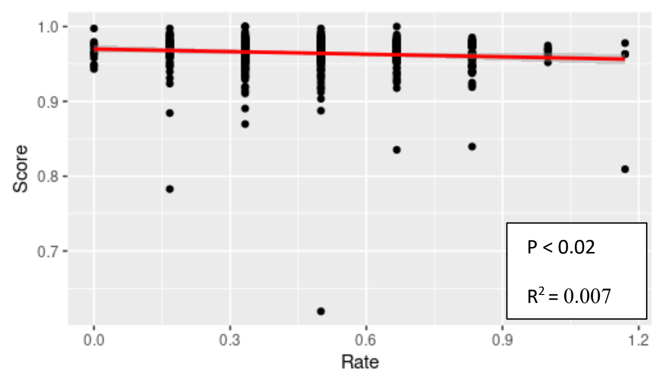

Fig 30: *Negative correlation between burst rate and motor performance (i.e. higher burst rate related to worse task accuracy).*

Score refers to task accuracy during Mov interval & Rate refers to burst rate (events/sec) of Mov interval.

Older group

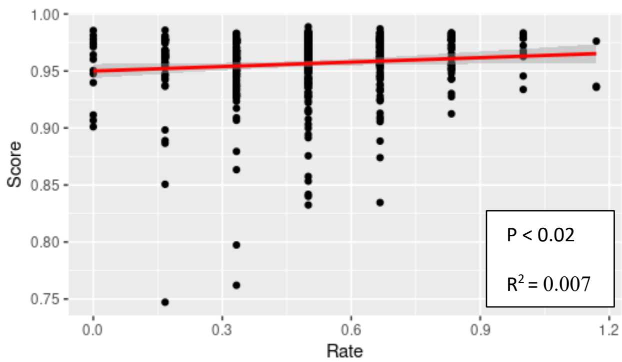

Fig 31: *Positive correlation between burst rate and motor performance (i.e. higher burst rate related to improved task accuracy).*

Score refers to task accuracy during Mov. interval & Rate refers to burst rate (events/sec of Mov interval.

No significant (*Bonferroni adjusted p* < 0.15) correlation between the task accuracy and all burst characteristics was found. However, regression analysis using individual burst characteristics revealed a significant (*Bonferroni adjusted p* < 0.02) but very week correlation (Adjusted R-squared: 0.007) between burst rate and task accuracy (see ***Fig 31***).

4.2.2.1.2 Post-movement Interval (Post)

No significant correlation between the task accuracy and burst characteristics was observed for either of the younger (*Bonferroni adjusted p* < 0.3) or the older group (*Bonferroni adjusted p* < 0.9).

4.2.2.1.3 Preparation Interval (Pre)

Younger group. No significant correlation between the task accuracy and burst characteristics was observed for the younger (*Bonferroni adjusted p* < 0.8).

Older group. Multiple regression analysis revealed a significant (*Bonferroni adjusted p* < 0.009) but weak correlation (Adjusted R-squared: 0.02) between the task accuracy and all burst characteristics. However, regression analysis using individual burst characteristics showed only burst amplitude was significantly (*Bonferroni adjusted p* < 0.002) correlated with the task accuracy (see ***Fig 32***).

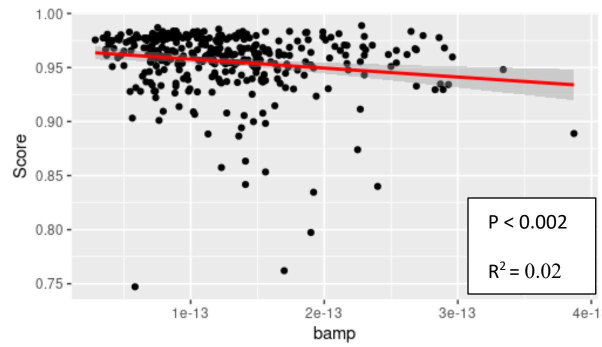

Fig 32: N*egative correlation between burst amplitude and motor performance (i.e. higher burst amplitude related to worse task accuracy).*

Score refers to task accuracy during Mov interval & bamp refers to burst amplitude during the Pre interval

4.2.2.2 Right Motor Area

Multiple regression analysis revealed a significant group effect in task accuracy (*Bonferroni adjusted p* < 0.001) during Mov interval. Therefore, the subsequent analyses were performed separately on younger and older subjects.

4.2.2.2.1 Movement Interval

No significant (*Bonferroni adjusted p* < 0.7) correlation between the task accuracy and burst characteristics was observed for both groups.

4.2.2.2.2 Post-movement Interval (Post)

Younger group. Multiple regression analysis revealed no significant (*Bonferroni adjusted p* < 0.1) correlation between task accuracy and burst characteristics.

Older group. We found a significant (*Bonferroni adjusted p* < 0.03) but weak correlation (Adjusted R-squared: 0.01) between task accuracy and all burst characteristics. Further, linear regression analysis using individual burst characteristics indicated that only amplitude was significantly (*Bonferroni adjusted p* < 0.01) correlated with the task accuracy (see ***Fig 33***).

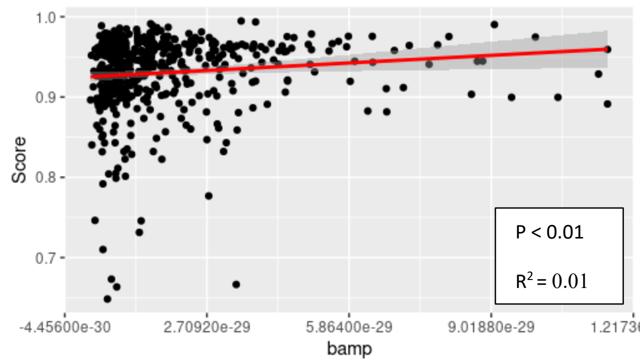

Fig 33: Positive *correlation between burst amplitude and motor performance (i.e. higher burst amplitude related to improved task accuracy).*

Score refers to task accuracy during Mov interval & bamp refers to burst amplitude of Post interval.

4.2.2.2.3 Preparation Interval (Pre)

Younger group. No significant (*Bonferroni adjusted p* < 0.4) correlation between the task accuracy and burst characteristics was observed for the younger group.

<u>Older group.</u> We found a significant (*Bonferroni adjusted p* < 0.03) but weak correlation (Adjusted R-squared: 0.01) between the task accuracy and combination of all the burst characteristics. Further, linear regression analysis was performed between the task accuracy and the three burst characteristics separately. Only the duration was significantly (*Bonferroni adjusted p* < 0.02) correlated with the task accuracy (see ***Fig 34***).

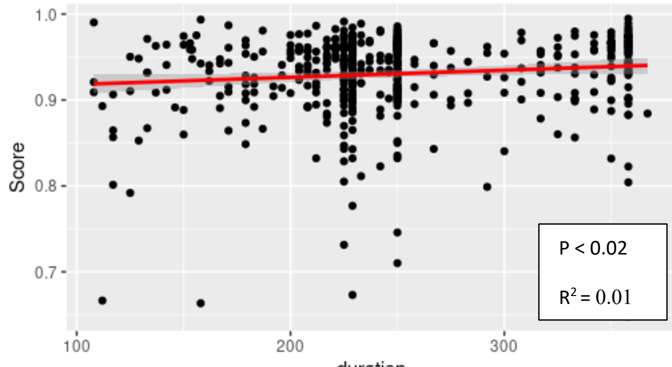

Fig 34*: Positive correlation between burst duration and motor performance (i.e. higher burst duration related to improved task accuracy).*

Score refers to task accuracy during Mov interval & duration refers to burst duration (ms) of Pre interval.

4.2.3 Resting state & Behavioural scores

The results from the behavioural assessments have been reported in detail in a previous publication from our group [26]. Briefly, significant differences between older and younger adults were found for both hands on the behavioural assessment scores for the 9HPT, BBT and PPT, where older adults performed significantly worse (*Bonferroni adjusted p* < 0.01). Therefore, subsequent regression analyses between burst characteristics collected at Rest and behavioural scores were performed separately on younger and older subjects.

4.2.3.1 PPT (Right Hand & Left Motor Area)

<u>Younger group.</u> We found no significant correlation (*Bonferroni adjusted p* $<$ 0.2) between the motor score and a combination of all the burst characteristics. Further, linear regression on individual characteristics showed that burst rate was significantly (*Bonferroni adjusted p* $<$ 0.04, Adjusted R-squared: 0.3) correlated with the PPT score (see ***Fig 35***).

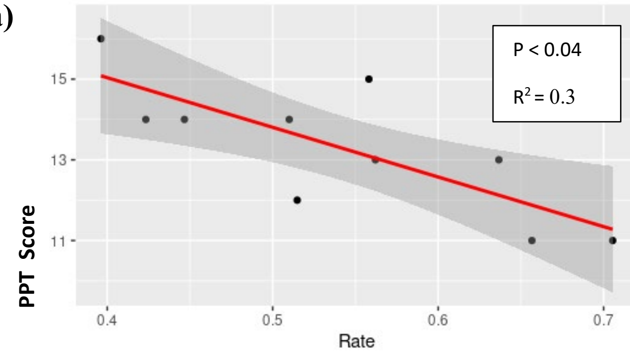

Fig 35: *Negative correlation between burst rate and PPT score (i.e. higher burst rate related to worse motor score).*

PPT score expressed as the number of pins placed into the board in 30 secs (right hand).

Rate refers to burst rate (events/sec) of resting state.

<u>Older group.</u> We found a significant (*Bonferroni adjusted p* $<$ 0.02) and strong correlation (Adjusted R-squared: 0.7) between the PPT score and burst characteristics. Further, linear regression on individual characteristics showed that only rate was significantly (*Bonferroni adjusted p* $<$ 0.007, Adjusted R-squared: 0.6) correlated with the PPT score (see ***Fig 36***).

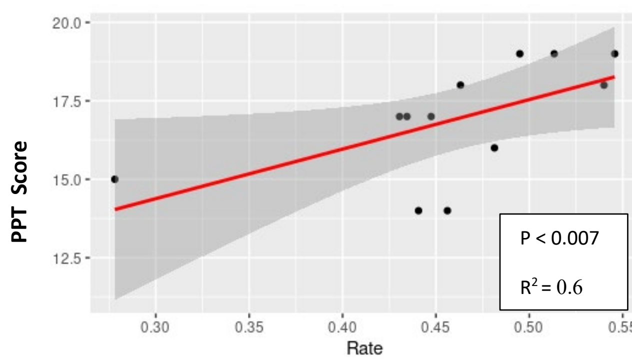

Fig 36: *Positive correlation between burst rate and PPT score (i.e. higher burst rate related to better motor score).*

PPT score expressed as the number of pins placed into the board in 30 secs (right hand).

Rate refers to burst rate (events/sec) of Rest.

4.2.3.2 NHPT (Right Hand & Left Motor Area)

Younger group. We found no significant (*Bonferroni adjusted p* < 0.09) correlation between the motor score and all burst characteristics. Further, linear regression on individual characteristics showed that burst rate was significantly (*Bonferroni adjusted p* < 0.01, Adjusted R-squared: 0.4) correlated with the NHPT score (see ***Fig 37***).

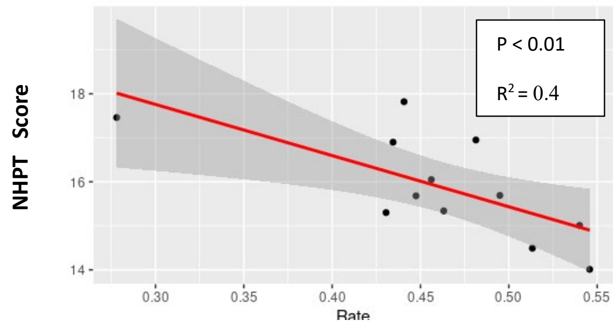

Fig 37: Negative *correlation between burst rate and NHPT score.*

NHPT score expressed as time (in secs) required to place and remove nine pegs from the board.

Rate refers to burst rate (events/sec) of resting state.

Older group. We found no significant (*Bonferroni adjusted p* < 0.4) correlation between the NHPT score and burst characteristics for the older group.

4.2.3.3 BBT (Right Hand & Left Motor Area)

Younger group. No significant (*Bonferroni adjusted p* < 0.6) correlation between the BBT score and burst characteristics was found in the younger group.

Older group. We found no significant (*Bonferroni adjusted p* < 0.07) correlation between the BBT score and burst characteristics for the older group.

4.3 Summary of the results obtained with the Threshold Method

A) Unimanual task

Comparison between groups (young vs. old). Among 3 burst characteristics, amplitude was only significantly different between the younger and older groups (see ***Table 11***).

Burst Characteristics	M1	M2	M3	Post	Rest	Pre
Rate	NS	NS	NS	NS	NS	NS
Amplitude	Old > Young	Old > Young	Old > Young	Old > Young	Old > Young	Old > Young
Duration	NS	NS	NS	NS	NS	NS

Table 11*. *Summary of burst characteristics comparison between groups. *'NS' =no significant difference between groups. Rate was similar in both the groups (top row), Amplitude was greater in older subjects (middle row) & duration was also similar in the two groups (bottom row).*

Comparison between intervals (young & old). Significantly different intervals are presented in the table below (***Table 12).***

Burst Characteristics	Move vs. Rest	Mov vs. Post	Between Movement (M1 vs. M2 vs. M3)
Rate	NS	M1 < Post M2 < Post M3 < Post	NS
Amplitude	M1 < Rest M2 < Rest M3 < Rest	M1 < Post M2 < Post M3 < Post	M2 < M1 M2 < M3
Duration	M1 – Rest (NS) M2 < Rest M3 – Rest (NS)	NS	NS

Table 12. Summary of between-interval burst characteristics comparison. *Burst rate (upper row), burst amplitude (middle row) & burst duration (bottom row). 'NS' = no significant difference between groups.*

B) Bimanual task (left M1)

<u>Comparison between group (young vs. old).</u> Burst amplitude was only found significantly different between the younger and older groups (see ***Table 13***).

Burst Characteristics	Mov	Post	Rest	Pre
Rate	NS	NS	NS	NS
Amplitude	Old > Young	Old > Young	Old > Young	Old > Young
Duration	NS	NS	NS	NS

Table 13. Summary of burst characteristics comparison between groups during the bimanual task. *'NS' refers to no significant difference between groups. Rate was similar in both the groups (top row), Amplitude was greater in older subjects (middle row) & duration was also similar in the two groups (bottom row).*

<u>Comparison between intervals (young & old).</u> Significantly different intervals are presented in the following table/ data from both groups.

Burst Characteristics	Mov vs. Rest	Mov vs. Post	Move vs. Prep
Rate	Mov < Rest	NS	Mov < Pre
Amplitude	NS	Mov < Post	NS
Duration	Mov < Rest	Mov > Post	Mov > Pre

Table 14. Summary of between-interval burst characteristics comparison*. Burst rate (upper row), burst amplitude (middle row) & burst duration (bottom row). 'NS' refers to no significant difference between groups.*

C) Bimanual task (right M1)

<u>*Comparison between groups (young vs. old).*</u> Burst amplitude only was significantly different between the younger and older groups (see ***Table 15***).

Burst Characteristics	Mov	Post	Rest	Pre
Rate	NS	NS	NS	NS
Amplitude	Old > Young	Old > Young	Old > Young	Old > Young
Duration	NS	NS	NS	NS

***Table 15**. **Summary of burst characteristics comparison between groups during bimanual task.** 'NS' refers to no significant difference between groups. Rate was similar in both the groups (top row), Amplitude was greater in older subjects (middle row) & duration was also similar in the two groups (bottom row).*

<u>*Comparison between interval (young & old).*</u> Significantly different intervals are presented in the ***Table 16***.

Burst Characteristics	Mov vs. Rest	Mov vs. Post	Move vs. Pre
Rate	Mov < Rest	Mov< Post	Mov < Pre
Amplitude	Mov < Rest	Mov < Post	Mov < Pre
Duration	Mov > Rest	Mov > Post	Mov > Pre

***Table 16. Summary of between-interval burst characteristics comparison**. Burst rate (upper row), burst amplitude (middle row) & burst duration (bottom row). 'NS' refers to no significant difference between groups.*

4.4 Comparison between Threshold Method & HMM Results

A) Unimanual task

Burst amplitude was significantly higher in older adults across all intervals for both HMM and threshold bursts. Summary of the comparison results in ***Table 17***.

Burst Characteristics	M1	M2	M3	Post	Rest	Pre
Rate	NS	NS	NS	NS	NS	NS
Amplitude	Old > Young (**)	Old > Young (**)	Old > Young (**)	Old > Young (**)	Old > Young (**)	Old > Young (**)
Duration	NS	NS	NS	NS	NS	NS

Table 17. Summary of burst characteristics comparison between groups during the unimanual task. *Significant between-group (young vs. old) comparisons obtained by both Threshold and HMM bursts are marked with '**', Non-significant between-group (young vs. old) comparisons are marked with 'NS'.*

B) Bimanual task (left M1)

Older adults exhibited higher burst amplitude across all intervals for both HMM and threshold bursts. The summary of the results is presented in ***Table 18***.

Burst Characteristics	Mov	Post	Rest	Pre
Rate	NS	NS	NS	NS
Amplitude	Old > Young (**)	Old > Young (**)	Old > Young (**)	Old > Young (**)
Duration	NS	NS	NS	NS

Table 18. Summary of burst characteristics comparison between groups during bimanual task. *Significant between-group (young vs. old) comparisons obtained by both Threshold and HMM bursts are marked with '**', Non-significant between-group (young vs. old) comparisons are marked with 'NS'.*

C) Bimanual task (right M1)

Burst amplitude was significantly higher in older adults across all intervals for both HMM and threshold bursts. Summary of the comparison results in ***Table 19***.

Burst Characteristics	Mov	Post	Rest	Pre
Rate	NS	NS	NS	NS
Amplitude	Old > Young (**)	Old > Young (**)	Old > Young (**)	Old > Young (**)
Duration	NS	NS	NS	NS

Table 19. Summary of burst characteristics comparison between groups during bimanual task. *Significant between-group (young vs. old) comparisons obtained by both Threshold and HMM bursts are marked with '**', Non-significant between-group (young vs. old) comparisons are marked with 'NS'.*

CHAPTER 5 - DISCUSSION

We examined the influence of healthy aging on beta bursts during two motor paradigms, unimanual and bimanual handgrips. Consistent with prior literature, we found greater burst amplitude in older adults across all movement intervals for both tasks. Age-related trends in burst characteristics were found to be consistent across both threshold and HMM methods. Further, we found that greater burst amplitude was associated with better motor performance during sustained muscle contractions. Our findings also showed that better behavioural assessment scores (e.g., NHPT, PPT, BBT) were related to reduced burst characteristics (rate & amplitude) at Rest.

5.1 Age-related changes in burst characteristics

Resting state. In line with our hypothesis, older adults exhibited significantly higher burst amplitude compared to their younger counterparts during resting-state. This agrees well with the increased resting-state beta power observed in bilateral M1 in older adults obtained from a previous MEG study [27]. The precise meaning of this increased burst amplitude in terms of the physiological role remains unknown as no previous studies to our knowledge have looked at the relationship between resting-state burst characteristics and motor outcomes. However, recent computational modeling studies have showed that bursts are generated due to the synchronous activation of a large population of pyramidal neurons by strong excitatory synaptic inputs from subcortical structures like the thalamus [39]. Therefore, the increased amplitude of beta bursts could be indicative of the higher degree of local neural synchronization in older adults. Further, resting-state burst characteristics have been extensively studied in the PD population, where it was shown that longer duration and higher amplitude bursts were predominantly present in these individuals during the ‘OFF’ medication period compared to the ‘ON’ medication period [40].

However, this elevated burst activity was mainly reported in the basal ganglia–thalamocortical (BGTC) motor network but not M1 [41]. Since we used non-invasive MEG recording for the study, it was beyond our scope to look at burst characteristics in subcortical structures of the BGTC motor network. Further studies on this topic are necessary to confirm if age-related changes in burst amplitude could be an early sign of PD.

<u>*Motor paradigms.*</u> As expected, we found significantly higher burst amplitude in older adults during the Mov and Post intervals, for both the unimanual and bimanual tasks. This is in line with a previous finding indicating older subjects exhibit higher absolute beta power throughout a movement task [27]. However, a recent study that investigated age-related changes in burst characteristics across all age groups (18–88 years), found a 'u-shape' relationship (see ***Fig 10***) for burst amplitude across all task intervals [47]. The authors showed that burst amplitude showed higher values in middle age compared to younger and older subjects. Since our study focused only on younger (19–28 years) and older (60-74 years) subjects, it was beyond our scope to investigate age-related trends in burst characterises across all age groups.

Further, we found no age-related differences in burst rate during task intervals (Pre, Mov & Post). This contradicts a previous study where it was shown that burst rate increases with age in pre-movement and decreases with age in post-movement intervals during a finger-tapping task [47]. This implies that age-related trends in burst rate could be specific to the type of motor task used.

Taken together, these findings show that, of the three burst characteristics studied, only burst amplitude displays consistent age-related patterns across all intervals of both the unimanual and bimanual tasks. Furthermore, neurofeedback and brain-computer interface technologies have recently been used to modulate brain signals [45, 46]. In this context, our findings imply that utilizing these systems to modulate burst amplitude could be the optimal way of improving motor function in older adults.

5.2 Modulation of burst characteristics between intervals

We compared burst characteristics between different task intervals of both motor paradigms, and the results were consistent across younger and older participants. This suggests that the deterioration in motor function reported in healthy ageing is not the result of an impairment in the capacity to modulate beta oscillations.

Rest vs. movement intervals. In accordance with our hypothesis, we found a significant decrease in some burst characteristics during movement intervals compared to the rest. However, the observed trend was not consistent across all burst characteristics. For instance, our results regarding the unimanual task show that burst amplitude during movement intervals was significantly less compared to the rest, but no difference in rate and duration between the two intervals was found. However, for the bimanual task, we found a decrease only in burst rate and duration during movement intervals. Distinct between-interval modulations in each burst characteristic suggest that various underlying brain networks generate different burst characteristics.

Post- vs. movement intervals. As expected, we found an increase in burst characteristics (rate & amplitude) during Post compared to Mov intervals. This is in line with previous studies reporting increased beta power during movement [27]. However, no prior evidence exists for higher burst characteristics to be the primary factor behind the increase in average beta power during PMBR. For instance, some studies have reported that biochemical factors, including GABAergic modulations in the motor network, can significantly affect beta power [55]. Therefore, future research on this topic is necessary to better understand the relationship between enhanced burst characteristics and elevated beta power.

Between movement intervals (M1 vs. M2 vs. M3). We found higher burst amplitude in sustained grip intervals (M1 & M3) compared to the unimanual task's dynamic intervals (M2). This is consistent with prior research that reported higher beta power associated with steady muscle contractions [27, 36]. Further, higher burst amplitude indicates that synchronous activation of a larger population of pyramidal neurons is required during steady contractions as opposed to dynamic contractions [36]. However, the functional significance of this higher burst amplitude is unclear, as few studies have examined the effect of elevated beta power on motor performance. Therefore, more research is needed to determine whether larger burst amplitude during sustained contractions affects motor function.

5.3 Relationship between burst characteristics & motor performance

5.3.1 Left M1

Movement interval. As expected, we found greater burst characteristics in terms of rate and amplitude that were related to better task accuracy during the sustained muscle contraction intervals of the unimanual task (i.e. movement intervals M1 & M3). Interestingly, we did not find such association during dynamic contraction (i.e. movement interval – M2). This suggests that burst characteristics during dynamic contraction have a more complex relationship with motor performance .

For the bimanual task, we found a similar trend, i.e. higher burst rate related to better task accuracy, but this was only present in the older group. Overall, our findings are consistent with earlier studies in which increased beta power was associated with better motor performance during visually-cued finger tasks [27].

<u>*Preparation interval.*</u> Contrary to our hypotheses, there was a relationship between reduced burst amplitude in the Pre interval and better task accuracy in older adults. A recent study by Simon *et al.*, reported that pre-movement burst characteristics (rate & amplitude) were related to response time but not task accuracy during a visually cued movement selection task [44]. However, this study only involved healthy younger participants (28 ± 8 years). This result implies that the relationship between pre-movement burst characteristics and motor performance is only present in older individuals. Another possibility is that impact of pre-movement burst characteristics on motor performance is task specific.

Collectively, our results suggest that lowering burst amplitude in the contralateral M1 during the movement preparation period could be preferred strategy to improve motor performance in the aging population.

5.3.2 Right M1

We further investigated the association between task accuracy and burst characteristics in the non-dominant motor area (i.e. right M1 for right-handed subjects) and found no association with any of the motor assessments. This suggests that bursts in the right M1 have limited on the performance on the ipsilateral hand during movement.

5.4 Resting-state burst characteristics & behavioural assessments

Older adults did not perform as well in the behavioral assessments (e.g. NHPT, BBT, PPT) compared to younger subjects, which is in line with a decline in motor function in older adults [1 - 4]. Further, we found that a lower Rest burst rate in the older group was associated with better PPT scores. However, no previous studies looked at the association between Rest burst characteristics and motor function in the context of healthy aging. Our results suggest Rest burst characteristics could be a reliable indicator of motor performance in the aging population.

It is worth mentioning that increased spontaneous or resting beta power is a signature of movement disorders (e.g. stroke & PD) [54]. This implies that a similar association between enhanced Rest burst characteristics and poorer motor performance is present in individuals with motor disorders. Future research is needed to better understand the relationship between burst characteristics and motor performance decline in neurological disorders.

5.5 Comparison between the threshold & HMM method results

As expected, we found a higher degree of overlap (around 83.5 %) between bursts identified by the two methods, which was further demonstrated by similar age-related trends observed in both methods, such as larger burst amplitude in older adults. Further, in line with our hypotheses, we found a less significant correlation between HMM-identified bursts and task accuracy (see ***Table 20 – 24*** in **Appendix IV**) during both the unimanual and bimanual tasks. Collectively, our results confirm that both the threshold and HMM methods were equivalently able to identify bursts from the beta band. However, the threshold method outperforms HMM in identifying bursts with more accurate physiological representations of brain activity related to the motor tasks. Although there is prior evidence of overlap between HMM and threshold bursts [42, 43], no study, to our knowledge, has compared the two methods in terms of their association with behavioural outcomes or motor performance.

The HMM method seemed to be fine-tuned more to improve its accuracy in extracting bursts. For instance, adding more hidden states or using different observation models (e.g. multinomial (discrete) emissions, Gaussian mixture emissions, or Time-delay embedded HMM [40, 41]) could improve this method. However, this would make HMM-based burst detection more complex and computationally demanding than the threshold method. Thus, our result suggests that in order to implement a real-time burst detector to modulate these bursts in aging or patient populations, the threshold method would be more advantageous than the HMM method.

LIMITATIONS

This is the first study that looked at the modulation of burst characteristics during hand movement in bilateral M1s in the context of healthy aging. There are several limitations to this study.

Previous studies suggested that resting beta power and MRBD are affected by the circadian rhythm (Toth et al., 2007; Wilson et al., 2014). However, in the MEG dataset, participants were scanned at different times of the day, including morning sessions (8 younger/6 older) and afternoon sessions (4 younger/6 older). Therefore, we cannot exclude circadian effects on the results due to differences in the scanning time.

It has been shown that pre-movement burst characteristics are associated with reaction time [44]. However, this was not investigated in our study because participants received no imperative instructions with respect to reaction time during motor tasks. Furthermore, our results showed a significant but weak correlation between burst characteristics and motor performance for both groups. For future studies, a more difficult task should be used to better discriminate the groups in terms of motor performance, as well as to reach a better understanding of its association with bursts.

Another noted limitation in the present study was a relatively smaller sample size (n = 24; 12 subjects in each group), which prevented us from analysing high-order (i.e. quadratic) age-related trends in MEG data. Thus, future neuroimaging studies with a larger number of participants would be necessary to model higher-order age-related trends and advance efforts towards a better understanding of the healthy aging human brain.

The inter-trial interval is a crucial factor to consider while developing protocols to study motor-related beta oscillations. Previous studies have reported that PMBR levels may interfere with the inter-trial baseline, leading to a possibly biased result [28]. Therefore, in this work, we used the resting-state beta power levels as the baseline to consider this issue.

CHAPTER 6 - CONCLUSION

Older adults exhibited significantly greater burst amplitude at rest as well as during movement and post-movement intervals. However, there were no age-related differences for other burst characteristics (rate & duration). We found an increase in burst amplitude during sustained muscle contractions compared to dynamic ones. Further, greater burst amplitude at Rest was associated with impaired motor performance in older adults, which further suggests that age-related trends in burst characteristics could be early indication of neurological disorders (e.g. PD).

Collectively, our results provide new insights into the effect of aging on transient beta bursts and their relationship with motor performance. This study is the first step toward developing a closed-loop neurofeedback system using a real-time burst detector to normalize brain oscillatory patterns for patients with motor deficits.

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APPENDICES

Appendix I: Comparison of bursts characteristics between interval during unimanual task

Table 2 - Posthoc results for burst rate (Unimanual):

Intervals	estimate	SE	df	t.ratio	p.value
M1 - M2	-0.0003766	0.013273	4565	-0.0283746	< 1
M1 - M3	-0.0002601	0.0133614	4565	-0.0194674	< 1
M1 - Post	**-0.0454586**	**0.0130386**	**4565**	**-3.4864527**	**<0.007**
M1 - Pre	**-0.1015347**	**0.0132141**	**4565**	**-7.683835**	**< 0.001**
M1 - Rest	0.0167358	0.0114282	4565	1.4644306	< 1
M2 - M3	0.0001165	0.013653	4565	0.0085332	< 1
M2 - Post	**-0.045082**	**0.0133372**	**4565**	**-3.3801551**	**< 0.01**
M2 - Pre	**-0.1011581**	**0.0135088**	**4565**	**-7.4883094**	**< 0.001**
M2 - Rest	0.0171124	0.0117677	4565	1.4541796	< 1
M3 - Post	**-0.0451985**	**0.0134253**	**4565**	**-3.3666761**	**< 0.01**
M3 - Pre	**-0.1012746**	**0.0135957**	**4565**	**-7.4490194**	**< 0.001**
M3 - Rest	0.0169959	0.0118674	4565	1.432152	< 1
Post - Pre	**-0.0560761**	**0.0132786**	**4565**	**-4.2230465**	**<0.001**
Post - Rest	**0.0621943**	**0.0115027**	**4565**	**5.4069196**	**< 0.001**
Pre - Rest	**0.1182705**	**0.0117012**	**4565**	**10.107537**	**< 0.001**

Table 2. Post hoc results for burst rate comparison between intervals

(Significant comparisons are marked with 'bold')

Table 3 - Posthoc results for burst amplitude (Unimanual):

Intervals	estimate	SE	df	t.ratio	p.value
M1 - M2	**1.44E-14**	**2.85E-15**	**4565**	**5.0435554**	**< 0.001**
M1 - M3	5.63E-15	2.87E-15	4565	1.9591217	< 0.7
M1 - Post	**-1.13E-14**	**2.80E-15**	**4565**	**-4.0126964**	**< 0.001**
M1 - Pre	8.26E-16	2.84E-15	4565	0.2908187	< 1
M1 - Rest	**-1.47E-14**	**2.46E-15**	**4565**	**-5.9683706**	**< 0.001**
M2 - M3	**-8.77E-15**	**2.94E-15**	**4565**	**-2.985901**	**< 0.04**
M2 - Post	**-2.56E-14**	**2.87E-15**	**4565**	**-8.9421152**	**< 0.001**
M2 - Pre	**-1.36E-14**	**2.91E-15**	**4565**	**-4.6710443**	**< 0.001**
M2 - Rest	**-2.91E-14**	**2.53E-15**	**4565**	**-11.48486**	**< 0.001**
M3 - Post	**-1.69E-14**	**2.89E-15**	**4565**	**-5.8469484**	**< 0.001**
M3 - Pre	-4.80E-15	2.92E-15	4565	-1.6427084	< 1
M3 - Rest	**-2.03E-14**	**2.55E-15**	**4565**	**-7.9532544**	**< 0.001**
Post - Pre	**1.21E-14**	**2.86E-15**	**4565**	**4.2295862**	**< 0.001**
Post - Rest	-3.42E-15	2.47E-15	4565	-1.3811966	< 1
Pre - Rest	**-1.55E-14**	**2.52E-15**	**4565**	**-6.1575223**	**< 0.001**

Table 3. Post hoc results for burst amplitude comparison between intervals

(*Significant comparisons are marked with ‘bold’)*

Table 4 - Posthoc results for burst duration (Unimanual):

Interval	estimate	SE	df	t.ratio	p.value
M1 - M2	3.6429429	1.949242	4565	1.8689021	< 0.926
M1 - M3	2.011966	1.962228	4565	1.0253476	< 1
M1 - Post	0.9995693	1.914824	4565	0.5220164	< 1
M1 - Pre	8.5137306	1.940587	4565	4.3871926	**< 0.001**
M1 - Rest	-0.3206515	1.678316	4565	-0.1910555	< 1
M2 - M3	-1.630977	2.005045	4565	-0.8134364	< 1
M2 - Post	-2.6433737	1.958677	4565	-1.3495709	< 1
M2 - Pre	4.8707876	1.983872	4565	2.455193	**< 0.02**
M2 - Rest	-3.9635944	1.728182	4565	-2.2935057	**< 0.03**
M3 - Post	-1.0123967	1.971601	4565	-0.5134897	< 1
M3 - Pre	6.5017646	1.996632	4565	3.2563653	**< 0.01**
M3 - Rest	-2.3326174	1.742816	4565	-1.3384189	< 1
Post - Pre	7.5141613	1.950064	4565	3.8532893	**< 0.01**

Table 4. Post hoc results for burst duration comparison between intervals

(Significant comparisons are marked with 'bold')

Appendix II: Comparison of bursts characteristics during unimanual task (left M1)

Table 5 - Posthoc results for burst rate (Bimanual – left M1):

Interval	estimate	SE	df	t.ratio	p.value
Mov - Post	-0.0810339	0.0147115	3786	-5.508221	**< 0.001**
Mov - Pre	-0.1693761	0.0157229	3786	-10.772605	**< 0.001**
Mov - Rest	-0.7096462	0.0133176	3786	-53.286313	**< 0.001**
Post - Pre	-0.0883422	0.0162292	3786	-5.443397	**< 0.001**
Post - Rest	-0.6286123	0.0139118	3786	-45.185503	**< 0.001**
Pre - Rest	-0.5402702	0.0149773	3786	-36.072572	**< 0.001**

Table 5. Post hoc results for burst rate comparison between intervals

(Significant comparisons are marked with 'bold')

Table 6 - Posthoc results for burst amplitude (Bimanual – left M1):

Interval	estimate	SE	df	t.ratio	p.value
Mov - Post	-1.98E-14	2.33E-15	3786	-8.4920347	**< 0.001**
Mov - Pre	-4.51E-15	2.49E-15	3786	-1.8086632	**< 0.001**
Mov - Rest	-6.09E-16	2.11E-15	3786	-0.2885613	**< 0.001**
Post - Pre	1.53E-14	2.57E-15	3786	5.9456175	**< 0.001**
Post - Rest	1.92E-14	2.21E-15	3786	8.7039114	**< 0.001**
Pre - Rest	3.90E-15	2.38E-15	3786	1.6421102	**< 0.001**

Table 6. Post hoc results for burst amplitude comparison between intervals

(*Significant comparisons are marked with 'bold')*

Table 7 - Posthoc results for burst duration (Bimanual – left M1):

Interval	estimate	SE	df	t.ratio	p.value
Mov - Post	-0.381353	1.769123	3786	-0.2155605	< 0.99
Mov - Pre	6.711186	1.890749	3786	3.5494857	**< 0.001**
Mov - Rest	-34.901836	1.601507	3786	-21.793126	**< 0.001**
Post - Pre	7.092539	1.951643	3786	3.6341366	**< 0.001**
Post - Rest	-34.520483	1.672963	3786	-20.63434	**< 0.001**
Pre - Rest	-41.613021	1.801094	3786	-23.104302	**< 0.001**

Table 7. Post hoc results for burst duration comparison between intervals

(*Significant comparisons are marked with 'bold')*

Appendix III: Comparison of bursts characteristics during unimanual task (right M1)

Table 8 - Posthoc results for burst rate (Bimanual – right M1):

Interval	estimate	SE	df	t.ratio	p.value
Mov - Post	-0.0810339	0.0147115	3786	-5.508221	**< 0.001**
Mov - Pre	-0.1693761	0.0157229	3786	-10.772605	**< 0.001**
Mov - Rest	-0.7096462	0.0133176	3786	-53.286313	**< 0.001**
Post - Pre	-0.0883422	0.0162292	3786	-5.443397	**< 0.001**
Post - Rest	-0.6286123	0.0139118	3786	-45.185503	**< 0.001**
Pre - Rest	-0.5402702	0.0149773	3786	-36.072572	**< 0.001**

Table 8. Post hoc results for burst rate comparison between intervals

(*Significant comparisons are marked with 'bold')*

Table 9 - Posthoc results for burst amplitude (Bimanual – right M1):

Interval	estimate	SE	df	t.ratio	p.value
Mov - Post	-1.98E-14	2.33E-15	3786	-8.4920347	**< 0.001**
Mov - Pre	-4.51E-15	2.49E-15	3786	-1.8086632	< 0.2
Mov - Rest	-6.09E-16	2.11E-15	3786	-0.2885613	< 0.9
Post - Pre	1.53E-14	2.57E-15	3786	5.9456175	**< 0.001**
Post - Rest	1.92E-14	2.21E-15	3786	8.7039114	**< 0.001**
Pre - Rest	3.90E-15	2.38E-15	3786	1.6421102	< 0.3

Table 9. Post hoc results for burst amplitude comparison between intervals

(Significant comparisons are marked with 'bold')

Table 10 - Posthoc results for burst duration (Bimanual – right M1):

Interval	**estimate**	**SE**	**df**	**t.ratio**	**p.value**
Mov - Post	-0.381353	1.769123	3786	-0.2155605	< 0.9
Mov - Pre	6.711186	1.890749	3786	3.5494857	**< 0.02**
Mov - Rest	-34.901836	1.601507	3786	-21.793126	**< 0.001**
Post - Pre	7.092539	1.951643	3786	3.6341366	**< 0.01**
Post - Rest	-34.520483	1.672963	3786	-20.63434	**< 0.001**
Pre - Rest	-41.613021	1.801094	3786	-23.104302	**< 0.001**

Table 10. Post hoc results for burst duration comparison between intervals

(*Significant comparisons are marked with 'bold')*

Appendix IV: Correlation between burst (HMM) characteristics & motor performance

Unimanual task (Young & Old) -

Interval	Analysis	*p* value
Pre	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Pre	0.54
M1	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at M1	0.75
M3	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at M3	0.06
Post	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Post	0.31

Table 20. No significant correlation between HMM burst characteristics & task accuracy during unimanual paradigm

Bimanual task (Left M1 - Young) –

Interval	Analysis	*p* value
Pre	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Pre	0.42
Mov	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Mov	0.29
Post	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Post	0.07

Table 21. No significant correlation between HMM burst characteristics & task accuracy during bimanual paradigm

Bimanual task (Left M1 - Old) –

Interval	Analysis	*p* value
Pre	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Pre	0.06
Mov	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Mov	0.82
Post	Multiple regression between task accuracy & burst characteristics (Rate + bamp + duration) at Post	0.35

Table 22. No significant correlation between HMM burst characteristics & task accuracy during bimanual paradigm

Resting state (Left M1 - Young) -

Task	Analysis	*p* value
PPT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.62
NHPT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.89
BBT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.53

Table 23. No significant correlation between Rest HMM burst characteristics & motor score

Resting state (Left M1 - Old) –

Task	Analysis	*p* value
PPT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.97
NHPT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.71
BBT	Multiple regression between motor score & burst characteristics (Rate + bamp + duration) at Rest	0.56

Table 24. No significant correlation between Rest HMM burst characteristics & motor score