CHANGES IN PHASE-AMPLITUDE COUPLING IN THE MOTOR NETWORK DURING HEALTHY AGING

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To my family

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CONTRIBUTION OF AUTHORS

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LingXin He conceived and performed data and statistical analysis on an existing dataset, designed the figures, interpreted the results from the new analyses, wrote and arranged the thesis manuscript.

Marie-Hélène Boudrias contributed to conceiving the study design, data collection, writing of the present manuscript.

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ABSTRACT

Background

Aging in the brain is associated with changes in information transfer efficiency, which can be quantified using magnetoencephalography (MEG) data. An emergent method to understand information flow in the brain is to evaluate phase-amplitude coupling (PAC), which estimates the statistical dependence of the phase of a low frequency with the amplitude of a higher frequency. It has been recently shown that theta-gamma PAC was important for cognitive functions and that this coupling was disrupted in aging. PAC in other frequency bands such as beta-gamma was also shown to be involved in motor functions. Since oscillations in the beta and gamma ranges are known to be affected in aging, this suggests that disrupted coupling due to aging could also be present in the brain motor network.

Objectives and Hypotheses

This study aims to (1) evaluate PAC in the motor network during initiation and execution of a visuomotor handgrip task, and (2) evaluate how PAC is affected by age.

We hypothesize that (1) PAC will be strongest during inter-trial/resting period and will uncouple at movement initiation / onset, (2) older adults will have stronger or longer coupling prior to motor initiation compared to young adults, and (3) disrupted PAC in older adults will be associated with greater deficits in motor performance.

Methods and Analysis

We used a cross-sectional design where 12 old and 12 young adults were recruited to take part in the experiment. The data was collected as part of previous study (Xifra-Porxas et al., 2019). All participants were healthy and right-handed and underwent motor and cognitive assessments. They performed a unimanual and a bimanual handgrip tracking tasks in the MEG scanner. Task accuracy was calculated from the distance between the subject's position on the screen and the target area. Participants repeated 50 trials of each motor task.

We selected the region of the brain with largest hand movement-related beta desynchronization in the sensorimotor cortex for each participant. PAC values were computed in the contralateral and ipsilateral primary motor cortex (cM1, iM1) using the

software Brainstorm. PAC was computed locally (within each M1) and inter-regionally (irPAC). The strength of coupling was extracted from the time-resolved PAC analysis during the preparation, initiation, and execution of handgrips. The coupling value was transformed to z-score values with respect to surrogate data generated to estimate strength of coupling. This last step was done for local PAC but not for irPAC.

We compared PAC over time between old and young adults using the two-sample t-test with the Statistical Parametric Mapping (SPM) method. We also compared differences in coupling strength across phases of the motor tasks and age using a two-way ANOVA. Lastly, we evaluated the association between motor performance and coupling strength with a Pearson's correlation factor. These statistics were performed for both unimanual and bimanual data.

Results

Overall, there was a difference in coupling between old and young adults in local PAC in cM1 and in the irPAC between the two M1s. Local coupling was higher in older adults; however, beta-low gamma irPAC showed the reverse effects, where younger adults had stronger coupling than older adults. The phases of the motor task affected PAC strength, although these effects were specific to gamma bands and brain areas. Most interestingly, there was a clear difference in directionality of beta coupling with the high gamma band, suggesting an information flow optimized in one direction. The beta band in cM1 was weaker at driving amplitude in iM1, but the beta band oscillations in iM1 were stronger at affecting gamma amplitude in cM1. Lastly, no significant differences were observed in PAC strength between old and young adults at any time point during the unimanual task.

In the bimanual task, we observed significant differences across age groups in local coupling within both M1s, but no difference between the different phases of the task. Older adults had stronger coupling with the high gamma, but not with the low gamma bands. Lastly, the association between accuracy on the task and respective coupling values had high variability, resulting in weak correlations between these 2 variables.

Conclusion

Beta-gamma coupling in the M1s is affected during aging, but coupling was not significantly related to the motor task. There is a directionality of information flow where beta band in iM1

was effective at modulating amplitude in cM1 during the motor task but not vice-versa. This result was only found in beta-high gamma coupling, which is known to play an important role during sensorimotor integration.

RÉSUMÉ

Contexte

Le vieillissement dans le cerveau est associé à des changements quant à l'efficacité du transfert d'information, qui peuvent être quantifiés à l'aide de données de magnétoencéphalographie (MEG). Une méthode émergente pour comprendre le transfert d'information dans le cerveau consiste à évaluer le couplage phase-amplitude (PAC), modalité qui estime la dépendance statistique de la phase d'une basse fréquence avec l'amplitude d'une fréquence plus élevée. Il a été récemment montré que le couplage thêta-gamma était important pour les fonctions cognitives et que ce couplage était affecté avec le vieillissement. Le couplage entre d'autres bandes de fréquences telles que la bêta-gamma s'est également avéré être impliqué dans les fonctions motrices. Étant donné que les oscillations dans les bandes bêta et gamma sont reconnues pour être affectées par le vieillissement, cela suggère le vieillissement pourrait également induire des changements dans le couplage de ces bandes dans le réseau moteur du cerveau.

Objectifs et hypothèses

Cette étude vise à (1) évaluer le PAC entre les fréquences beta et gamma dans le réseau moteur pendant l'initiation et l'exécution d'une tâche visuomotrice consistant en des contractions isométriques de la main, et (2) évaluer comment le couplage est affecté par l'âge.

Nous émettons l'hypothèse que (1) le couplage sera plus fort pendant la période de repos et se découplera à l'initiation du mouvement, (2) les adultes plus âgés auront un couplage plus grand ou plus long avant l'initiation du mouvement par rapport aux jeunes adultes, et (3) le couplage perturbé chez les personnes âgées sera associé à des déficits plus importants en termes de performance motrice.

Méthodes et analyse

12 adultes âgés et 12 jeunes adultes ont été recrutés pour participer à cette étude. Les données ont été collectées dans le cadre d'une étude antérieure (Xifra-Porxas et al., 2019). Tous les participants étaient droitiers, en bonne santé. Leurs fonctions motrices et cognitives ont été évaluées avant la collecte de données dans le scanner. La tâche motrice consistait à moduler la force de contraction d'une ou des deux mains afin de faire bouger un point (Fig. 1) et

d'atteindre la zone cible affichée sur l'écran dans le scanner MEG. La précision de la tâche a été calculée à partir de la distance entre la position sur l'écran et la zone cible. Les participants ont répété 50 essais lors de chaque tâche motrice.

Nous avons sélectionné la région du cerveau avec la plus grande désynchronisation bêta liée au mouvement dans le cortex sensoriel-moteur primaire de la région de la main pour chaque participant. Les valeurs de PAC ont été calculées dans le cortex moteur primaire controlatéral et ipsilatéral (cM1, iM1) par rapport à la main droite à l'aide du logiciel Brainstorm. Le PAC a été calculé localement (dans chaque M1) et entre les deux cortex moteurs (PAC interrégional, irPAC). L'intensité du couplage a été calculé pendant la préparation, l'initiation et l'exécution des tâches motrices. L'intensité du couplage a été transformé en statistique z-score obtenu par rapport aux données de substitution générées dans Brainstorm. Cette dernière étape a été faite pour le PAC local mais pas pour le irPAC.

Nous avons comparé le PAC en fonction du temps entre les adultes âgés et jeunes en utilisant des tests-t avec la méthode de Statistical Parametric Mapping (SPM). Nous avons également comparé le couplage avec le temps et l'âge comme effets principaux à l'aide d'une ANOVA double. Enfin, nous avons évalué le lien entre les performances motrices et le PAC à l'aide du facteur de corrélation de Pearson. Ces statistiques ont été réalisées pour les données uni- et bimanuelles.

Résultats

Dans l'ensemble, nous avons observé une différence de PAC local entre les adultes âgés et jeunes dans le cM1 et de l'irPAC entre les deux M1s. Le couplage local était plus élevé chez les adultes âgés; cependant, nous avons observé l'effet inverse pour le l'irPAC dans la bande gamma basse, les jeunes adultes ayant un couplage plus élevé que ceux âgés en général. Les phases de la tâche motrice ont affecté l'intensité du couplage, bien que ces effets soient spécifiques aux bandes gamma et aux zones cérébrales. Surtout, il y avait une différence claire quant à la direction de l'intensité du couplage dans la bande gamma élevée, suggérant un transfert d'information optimisé dans une direction. La bande bêta dans le cM1 était moins couplée à l'amplitude de la fréquence gamma dans l'iM1, mais les oscillations de la bande bêta dans l'iM1 étaient plus couplées avec l'amplitude de la fréquence gamma dans le cM1.

Enfin, aucune différence significative n'a été observée pour le PAC entre les adultes âgés et jeunes au cours de la tâche uni-manuelle.

Pour la tâche bimanuelle, nous avons observé des différences significatives entre les 2 groupes en termes de couplage local dans les deux M1s, mais le PAC n'était pas affecté par les phases de la tâche motrice. Les adultes âgés avaient un couplage plus prononcé dans la bande gamma élevée, mais pas dans les bandes gamma basses. Enfin, une forte variabilité a été observée entre la performance de la tâche et les valeurs de couplage respectives, entrainant une faible corrélation entre ces deux variables.

Conclusion

Le couplage bêta-gamma dans les M1s est affecté au cours du vieillissement, mais il n'y avait pas de tendance temporelle cohérente: en d'autres termes, le couplage n'était pas significativement lié à la tâche motrice. Une directionnalité dans le transfert d'information a été observé, la bande bêta dans l'iM1 plus étant efficace à moduler l'amplitude gamma dans le cM1 pendant la tâche motrice. Ce résultat n'a été trouvé que dans la bande gamma élevée, qui est connue pour jouer un rôle important durant l'intégration sensorimotrice.

PREFACE

The content of this thesis will include the following chapters:

Chapter 1: In this chapter, we present an overview of aging in the brain, common neuroimaging techniques and theoretical understanding of phase-amplitude coupling. It explores the literature gap and gives the rationale for the project, the resulting objectives and hypothesis.

Chapter 2: This chapter provides a description of the methodology for the study.

Chapter 3: The results of the project will be presented in this chapter.

Chapter 4: In this chapter, we provide a discussion of our findings and how they relate to other studies in the field.

Chapter 5: Here, we leave the reader with final comments and future directions for this research.

Chapter 6: list of references

Chapter 7: list of appendices

CHAPTER I | INTRODUCTION

BACKGROUND

Aging

The rapid growth of the aging population is an alarming cause for concern. The prevalence of disability rises with age (Division, 2013), increasing the costs on the healthcare system (Khan et al., 2012). The burden of the aging population on society is high due to the increased costs in disability care and reinforces the importance of researching methods to help maintain their motor and cognitive capabilities.

Normal aging is associated with neurodegenerative and neurochemical changes in the brain, accompanied by a progressive decline in cognitive performance, which is particularly evident in motor ability (Goh, 2011). In the motor domain, older adults tend to have slower movement speeds, difficulties with coordination and reduced accuracy across various types of motor tasks (Seidler et al., 2010). During motor learning, older adults have also be shown to have poorer long-term retention of motor skills as well as increased susceptibility to interference during memory consolidation as compared to younger adults (Roig et al., 2014).

Regeneration of brain tissue in adults is limited. The neuronal cell loss observed during aging is thought to be associated with brain reorganization in terms of brain connectivity (Castelli et al., 2019). This reorganization leads to functional changes in the brain, which can be quantified via neuroimaging techniques such as electroencephalography (EEG) or magnetoencephalography (MEG).

Motor network & Aging

Over the past decades, many brain areas involved in the production of movement have been identified in the human brain (Hardwick et al., 2018). During movement execution, there is bilateral activation of the **primary motor area** (M1) and **primary sensory** cortex (S1), the **dorsal** and **ventral premotor cortex** (dPMC, vPMC), the **supplementary motor area** (SMA), the cingulate cortex, the **inferior parietal lobule** (IPL), the thalamus, as well as the putamen and cerebellum (Hardwick et al., 2018). The activation is most important on the left hemisphere in right-handed subjects. M1 in particular, has been found to have a prominent role in motor planning and execution (Engel & Fries, 2010; Heinrichs-Graham & Wilson,

2015; Pogosyan et al., 2009). M1 is also known to contain corticospinal neurons, which are important players in the production of hand movement (M.-H. Boudrias et al., 2010; Lemon, 2010; Rathelot & Strick, 2009).

During aging, functional reorganization of brain activity is characterized by **increased recruitment of brain areas**, particularly higher order sensory processing and cognitive areas (Goble et al., 2010; Heuninckx et al., 2005). Additional recruitment of brain areas in aging include the parietal areas, which are key to visuospatial processing during motor planning (Fogassi & Luppino, 2005), and the frontal cortices (including the SMA, the vPMC and the dorsolateral prefrontal cortex (DLPFC)), which are involved in motor planning and decision-making (Goble et al., 2010; Ward & Frackowiak, 2003).

There is also a **decreased lateralization** of task-related M1 activation (M. H. Boudrias et al., 2012; Talelli et al., 2008; Ward & Frackowiak, 2003). An increased activation in the ipsilateral cortex is also observable in older individuals when compared to younger ones during the performance of an unimanual task (Ward & Frackowiak, 2003). This change is thought to be mediated by reduced intracortical inhibition from the contralateral M1 to the ipsilateral M1 (M. H. Boudrias et al., 2012; Talelli et al., 2008). This suggests that greater bilateral M1 activation is a key marker of aging in the brain during motor performance.

On top of recruiting additional brain areas during tasks, the aging brain also shows **changes in connectivity and information transfer efficiency**. In a study by (Park et al., 2012), which used functional magnetic resonance imaging (functional MRI, fMRI) during a dominant/non-dominant handgrip task, it was shown that age affected the efficiency of information transfer globally and locally. Global efficiency was most affected in aging during non-dominant hand use, which was attributable to impaired information transfer between hemispheres and within the ipsilateral hemisphere to the moving hand but not the contralateral one. These results indicate that functional brain changes in aging may be due to change in the information transfer capacity within the motor networks, both in the ipsilateral hemisphere and between hemispheres (Park et al., 2012).

Neuroimaging modalities

Functional Magnetic Resonance Imaging (fMRI)

Most studies presented above have used fMRI to detect which brain regions are activated during motor tasks. fMRI measures brain activity indirectly: increased neuronal activity requires increased oxygenation; hence the active brain region will receive more oxygen from the blood. fMRI functions by capturing the contrast of blood oxy- and deoxy-hemoglobin, which can indirectly infer to the changes in blood flow to a region of the brain. This fMRI measure is called the blood-oxygen-level-dependent (BOLD) response. The BOLD response is slow, thus cannot capture fine temporal aspects of brain activity. However, this aspect is crucial to understand the underlying network activity. As such, we want to know not only *which* brain regions are active and *whether* they interact, but also *how* they interact with each other. Modalities with higher temporal resolution such as MEG / EEG may provide insights in this domain.

Magneto/Electroencephalography (MEG/EEG)

MEG and EEG modalities are used to record electrical activity from the brain at high temporal resolution. These modalities have the capability to measure synchronous activity of different neuronal populations. MEG has the additional advantages of being able to detect reliably oscillations in the higher frequency bands, as it is less affected by muscle activity artifacts in comparison to EEG (D. O. Cheyne, 2013; Whitham et al., 2007).

Five major frequency bands can be observed in the brain, each band being present during specific behavioural states. A review of the physiological roles of each frequency band can be found in (Assenza et al., 2017). Briefly:

Delta (<4Hz): is the most prominent rhythm during non-rapid eye moment sleep. It is seldom observed in non-pathological awake conditions but may be present after traumatic events to the brain (e.g., stroke, physical damage).

Theta (4-8Hz): is involved in memory tasks and the consolidation process during sleep. It is mainly observed in frontal and hippocampal brain areas.

Alpha (Mu, 8-12Hz): is involved in attention and vision networks and plays an inhibitory role, for instance increased power in the alpha band is thought to promote inhibition of task-relevant brain areas.

Beta (12-30Hz) oscillatory activity is involved in the suppression of voluntary movement (Pfurtscheller & Lopes Da Silva, 1999). Brain beta power decreases during movement, an event called movement-related beta desynchronization (MRBD) (Pfurtscheller & Lopes Da Silva, 1999). It is present in the sensorimotor brain areas (primary motor cortex (M1) and primary sensory area (S1)).

Gamma (30-90Hz): is involved in facilitating synchronization in a neuronal population, as well as in information transfer mechanisms during sensorimotor integration, learning and other cognitive processes.

In this study, we choose to focus on beta and gamma bands as it is well established these bands are playing an active role in motor performance (Nowak et al., 2017, 2018; Xifra-Porxas et al., 2019). We also focused on M1, which is an area known to be affected by aging processes (see Section *Brain Waves & Aging*).

How does fMRI studies inform MEG-based ones?

In the studies cited above, fMRI has been the main neuroimaging modality used to study motor network in aging. However, a question remains: can we reliably use the brain regions identified using this modality during handgrip tasks to base our MEG / EEG analyses on? Both modalities capture fundamentally different aspects of brain activity: fMRI's BOLD response comes from the changes in blood oxygenation whereas MEG / EEG detect principally magnetic or electrical brain activity.

For EEG:

Many studies have evaluated how the underlying brain activity recorded with EEG correlate to the BOLD fMRI response. Local field potential (LFP) recorded in the occipital lobe of monkeys simultaneously with BOLD signal in the MRI scanner have revealed that both signals are positively correlated with each other (Logothetis et al., 2001). As EEG primarily relies on detecting scalp LFP, this supports the idea that the results from fMRI studies can be used as references for EEG studies when choosing a region of interest within the brain.

For MEG:

In a study by (Lankinen et al., 2018), subjects had their brain activity recorded twice using both fMRI and MEG modalities while watching a black-and-white movie. It was shown that direct voxel-wise comparison between MEG and fMRI signals were not correlated significantly. However, by applying a spatial-filtering approach to derive canonical values from the MEG data, the authors were able to 1) derive a matrix from MEG data, which increased consistency in brain signals *across* subjects and 2) use these derived values to find associations in cortical activity between the MEG and fMRI recordings. Overall, they found that the derived-MEG signals were associated with the fMRI ones for the following combinations: 1) in the occipital lobe for all frequencies except between 13-23 Hz, and 2) in the frontal and temporal regions for frequencies below 8 Hz and between 55-100Hz.

Thus, even without the exact location of M1, the approximate brain area found with BOLD activation seemed to correlate with invasive neurophysiology studies. In other words, the BOLD activations represent actual neuronal activation, henceforth justifying the use of MEG to study motor areas identified using fMRI. MEG is thus suitable to understand neuronal coupling within and across active brain regions during a motor task.

Brain waves & Aging

Beta band

Beta band oscillations in M1s are involved in the maintenance of a steady state (Engel & Fries, 2010). The steady state is defined as a state of no change, hence either at rest or when holding an isometric contraction. Thus, the beta band is present when maintaining a current brain state. It has been demonstrated that entraining brain rhythms at the beta rhythm with a brain stimulation at 20Hz over M1 induced slower movements in healthy adults when they performed a tracking task with a joystick (Pogosyan et al., 2009). This suggests that the desynchronization in the beta band plays a role in movement planning.

Furthermore, beta-band activity seems to be dependent on the age. During **aging**, MRBD as well as resting beta power are compromised: MRBD amplitude in M1 obtained during an unimanual grip task and beta power at rest were shown to be higher in older adults (Rossiter et al., 2014). Increased MRBD in M1 were also shown to be correlated with worse motor task

performance (Xifra-Porxas et al., 2019). Modulation in brain oscillatory patterns in the beta band can thus impact movement performance.

A recent study using MEG has looked at the effect of age on beta oscillations during movement planning and execution in developing children aged 9 to 15 years old (Heinrichs-graham et al., 2020). Interestingly, in children, beta activity in the right parietal lobe and not in the motor cortices predicted reaction time during either planning or execution. In the parietal cortex, increasing age was associated with increased MRBD but subsequently, shorter reaction times (Heinrichs-graham et al., 2020). Hence, increased MRBD in the parietal cortex in young children seem to be related to better motor performance whereas in older adults, increased MRBD in M1 seem to worsen performance. This suggests that activity in the beta band is important for motor performance and is affected by age, where in older adults, beta activity that predicts reaction time seem to shift to the sensorimotor areas and particularly to M1 (M. H. Boudrias et al., 2012; Talelli et al., 2008; Ward & Frackowiak, 2003; Xifra-Porxas et al., 2019).

Gamma band

Gamma oscillations are more temporally and spatially resolved in the timing and location of its appearance than other rhythms involved in movement (Miller et al., 2009). Specifically, gamma oscillations in M1 peak shortly after movement initiation (D. Cheyne et al., 2008; Muthukumaraswamy, 2010) and can reliably represent individual finger movements (Miller et al., 2009). The increase in gamma power during movement initiation and execution is termed movement-related gamma synchronization (MRGS). MRGS is more lateralized to the contralateral M1, unlike beta band activity (Gaetz et al., 2011). The role of gamma oscillations in M1 has been proposed to represent active motor control processes during execution (Butorina et al., 2014; Nowak et al., 2018).

Changes in the gamma band across age have also been reported. Gamma frequency and power was shown to decrease with age during a visual cartesian grating presentation and visuospatial discrimination tasks (Murty et al., 2020; Wiesman & Wilson, 2019). In the motor domain, MRGS frequency was shown to decrease with age in adults from 20 to 45 years of age in M1 (Gaetz et al., 2011).

The evidence so far suggests that beta and gamma bands play important roles across movement stages, that they are changing throughout age and that these changes are heavily taking place in M1 (Gaetz et al., 2011; Rossiter et al., 2014). As both beta and gamma bands were shown to be involved in motor tasks, we decided to direct our focus on these two frequencies for this study.

Phase-Amplitude Coupling (PAC)

It is widely accepted that information processing in the brain is related to synchronous neuronal activity, both within regions and frequencies as well as across. This synchronization is thought to be the basis of neuronal communication and information transfer at selective time windows (Fries, 2005; Womelsdorf et al., 2007). In the iconic paper by Fries published in 2005 on the communication-through-coherence (CTC) hypothesis, the author postulated that neuronal coherence is a mean of effective communication between two neuronal groups, whereas the lack of coherence between neuronal groups implies inefficient or inexistent communication.

Excitability of neuronal groups is modulated by rhythmic oscillations (Jacobs et al., 2007). At a specific phase of the oscillation, the neurons are more excitable thus more 'open' to both receiving and transmitting information. When input in the form of action potentials arrive at this phase, this neuronal group is most receptive. Hence, when two neuronal groups synchronize their respective opening time windows, information is transmitted more efficiently between them. Timing information to arrive during this opening window is crucial for efficient information transfer. Conversely, when the neuronal groups are out of synch, it is less likely that information is received and transmitted. Hence, asynchronous activity can be understood as a form of gating of information. A recent reformulation of the CTC exists, which addresses the challenges of the original CTC (Fries, 2015), but the main idea remains unchanged.

<u>What does synchronization actually mean?</u>

There are different types of neuronal synchronization that can be measured using MEG / EEG modalities thanks to recent advances in computational power (Canolty & Knight, 2010). A brief review of the main types of synchronous neuronal activity studied is presented here.

The reader is directed to the review (Canolty & Knight, 2010) for a more comprehensive review.

Synchronous neural activity can be observed across both spatial and temporal scales. Phase to phase coupling in the same bandwidth is observed in different areas of the brain. *This cross-location, same frequency phase coupling* is stipulated to have an important role in regulating communication between areas, whereas *same location, cross-frequency coupling* (CFC) is understood as being an intrinsic brain mechanism for integration of information across temporal scales (Palva et al., 2005).

Phase-amplitude CFC has also gained increasing interest in recent years. Computationally, PAC is an estimate of the statistical dependence between the phase φ_{f_φ} of a lower frequency f_φ and the amplitude A_{f_A} of a higher frequency f_A. In the neurophysiological context, PAC can be understood as part of the CTC hypothesis (Fries, 2005; Gonzalez et al., 2020), where the phase of the lower frequency can modulate excitability of a neuronal group, creating transient openings for information flow. During these openings, the synchronization of higher frequencies is facilitated. This transient coupling of low frequency phase and high frequency power thus has a functional interpretation, coherent within the CTC hypothesis. Generally speaking, PAC is thought to reflect processes underlying information gating and communication across networks (Siegel et al., 2012).

Synchronization within and across areas

PAC can be computed either within a single brain area and across many areas. When PAC is recorded within a single area (local PAC), it is understood as f_φ drives power in f_A. It is implied that the phase of the lower frequency drives the amplitude of the higher frequency.

When estimating the statistical dependence of φ_{f_φ} to A_{f_A}across areas (inter-regional PAC, irPAC), the inferred directionality is that φ_{f_φ}drives A_{f_A}, but this is not necessarily true in all conditions (Nandi et al., 2019). In a study by Nandi et al. (2019), the authors argued that A_{f_A}, which represent spiking activity of a "driver" neuronal group, can arrive in bursts to a "receiver" group, thus creating a low-frequency oscillation in the post-synaptic membrane of the receiver group. The driver network has PAC in local network, thus transmitting the same to the receiver network. This kind of directionality can hold for excitatory networks such as

the hippocampal-prefrontal cortex network but may not be applicable when both areas send inhibitory projections to each other, such as the bihemispheric connections between both M1s.

When estimating irPAC where the phase φ_{f_φ} modulates the amA_{f_A}, it is often assumed that the lower frequency f_φ is more widespread across brain areas. In this case, coupling reflects increased transient and specifically targeted information transmission, which is functionally relevant (Canolty & Knight, 2010).

Disorders involving PAC

PAC can be observed in the hippocampus, basal ganglia, and neocortex across species. Theta-gamma and alpha-gamma PAC was shown to be involved in attention (Szczepanski et al., 2014), working memory (Reinhart & Nguyen, 2019), visual motion detection (Händel & Haarmeier, 2009) and learning (Tzvi et al., 2018). The f_φ was also shown to change with cognitive load in working memory tasks (Axmacher et al., 2010). The influence of each f_φ is dependent on the brain area and the task. Hence, given the involvement of beta and gamma bands in motor performance in the motor cortices, it is natural to question whether they are coupled in the motor cortex. Beta-gamma PAC was shown to be affected in Parkinson's Disease, where motor performance is impaired (De Hemptinne et al., 2013) as well as in autistic children (An et al., 2021).

In the context of aging, a recent study showed that disruption in PAC was associated with deficits in cognitive performance (Reinhart & Nguyen, 2019). In this study, older adults had uncoupled theta-gamma rhythms when performing working memory task paradigm. It was also shown that these changes were reversible since applying transcranial alternating current stimulation (tACS) in the theta rhythm helped re-couple PAC in the theta-gamma band, which improved working memory. Whereas specific coupling of brain oscillatory patterns is important for cognitive performance, it remains unknown how important they are in the context of motor performance.

RATIONALE / LITERATURE GAP

Aging is associated with functional brain changes, which affects the motor network and performances (Goh, 2011). There is also evidence that oscillatory patterns are affected by

aging. For instance, theta-gamma PAC was shown be affected by age and the disruption of this coupling had an impact on the performance on a working memory task (Reinhart & Nguyen, 2019). In the motor domain, an increased activation in M1 during hand task is observed in older adults (M. H. Boudrias et al., 2012; Talelli et al., 2008; Ward & Frackowiak, 2003). Aging has also an impact on beta and gamma bands activity across movement stages within these areas (Gaetz et al., 2011; Rossiter et al., 2014; Xifra-Porxas et al., 2019). However, the way they are coupled during movements remains unknown in the healthy aging population. How their direct interaction affects motor performance and how it is influenced by age also remains to be studied.

OBJECTIVES

This study's aims were to (1) evaluate temporal changes in PAC in M1 during initiation and execution of visuomotor handgrip tasks, and (2) evaluate how the changes in PAC are affected by age.

HYPOTHESES

When beta power is higher (at rest, and in older adults compared to younger adults) and gamma power is lower, such as during motor planning, we expected to see stronger coupling between the two bands. In contrast, when gamma power is higher and beta power is lower, such as when movement is initiated, we expected to see weaker coupling.

Hence, since beta power at rest is higher than during movement, that it is also higher in older adults compared to younger adults, we expected to see stronger or longer coupling during motor planning (before movement initiation). We also expected that this effect is enhanced in older compared to younger adults.

Therefore, we **hypothesized** that (1) PAC would be stronger during the resting period and would uncouple at movement onset, (2) older adults would have stronger or longer coupling prior to movement onset compared to younger adults, and (3) disrupted PAC in older adults would be associated with greater deficits in motor performance.

CHAPTER II | METHODOLOGY

STUDY DESIGN

A dataset collected from a study previously performed in our laboratory was used for this study. The details about participants recruitment, data collection and data preprocessing can be found in (Xifra-Porxas et al., 2019). To reiterate:

Participants

Data was collected from 24 subjects (12 young, 12 old). All data was collected at the MEG facility at the McConnell Brain Imaging Center (BCI) of the Montreal Neurological Institute (MNI). Age, handedness and medical history were collected as demographic information from participants. Motor ability of both hands were characterized using the Nine Hole Peg Test (9HPT) (Virgil Mathiowetz et al., 1985), Box and Blocks Test (BBT) (V. Mathiowetz et al., 1985), Purdue Pegboard Test (PPT) (Lindstrom-Hazel & VanderVlies Veenstra, 2015), and Hand Grip Strength (HGS) (Peolsson et al., 2006). This was done in order to characterize a wide range of upper limb motor functions, from manual dexterity to strength. Participants were also screened for their cognitive status using the Mini-Mental State Examination (MMSE, (Folstein et al., 1975)).

Inclusion criteria

- Age: between 18 and 30 for young adults, and over 60 for older adults.
- Right-Handed: a score of at least 74 on the Edinburgh handedness Inventory.

Exclusion criteria

- Medical history of neurological and psychiatric disorder
- MEG exclusion criteria: presence of ferromagnetic material such as metal implants, crowns, dental braces, etc.

Characterization of the sample

- **9 Hole Peg Test (9HPT)** (Virgil Mathiowetz et al., 1985): This assessment measures finger dexterity. Participants need to remove and place nine pegs from a container into holes of a board as fast as possible. The result is measured in seconds and reflects their speed.

- **Box & Blocks Test (BBT)** (V. Mathiowetz et al., 1985): This assessment measures gross manual dexterity unilaterally. It consists of moving as many blocks from one container to another as possible within 60 seconds. The result is measured as the total number of blocks displaced.
- **Hand Grip Strength (HGS)** (Peolsson et al., 2006): This assessment measures grip strength. Participants have to perform 3 maximal force contractions with each hand using a dynamometer. The HGS is measured in kilograms.
- **Purdue Pegboard Test (PPT)** (Lindstrom-Hazel & VanderVlies Veenstra, 2015): This test is designed to assess two motor functions: the gross movement of the fingers, hand and arm, and fingertip dexterity. Gross movement is quantified as the number of pins placed into the holes of a board within 30 seconds. Fingertip dexterity is quantified as the number of pins, collars and washers assembled within 60 seconds using both hands.
- **Mini-Mental State Examination (MMSE)** (Folstein et al., 1975): This test is designed as a screening tool for cognitive impairment by testing users on various mental tasks. Briefly, the MMSE measures orientation, immediate recall, short-term verbal memory, calculation, language, and construct ability.

Experimental Flow

Participants first underwent eligibility screening as described previously. Then, participants were familiarized with the motor tasks before beginning the MEG recordings. All participants followed the same protocol inside the MEG scanner: MEG signal was recorded while subjects performed two motor tasks interspersed between three 5-minutes resting-state recordings (RS). During the RS recordings, participants were asked to stare at a white cross displayed on the screen and to not think of anything specific nor move. After the first RS, each subjects' maximum voluntary contraction (MVC) was obtained before proceeding to the motor tasks. Subjects underwent first an unimanual right handgrip task, followed by a bimanual handgrip one. Both tasks consisted of squeezing the gripper(s) from rest to 15% of their MVC, and then to 30% of their MVC in the unimanual task, such that the circles stay in the target white ramp (Fig. 1). The order of the tasks was not counter balanced.

Description of motor tasks

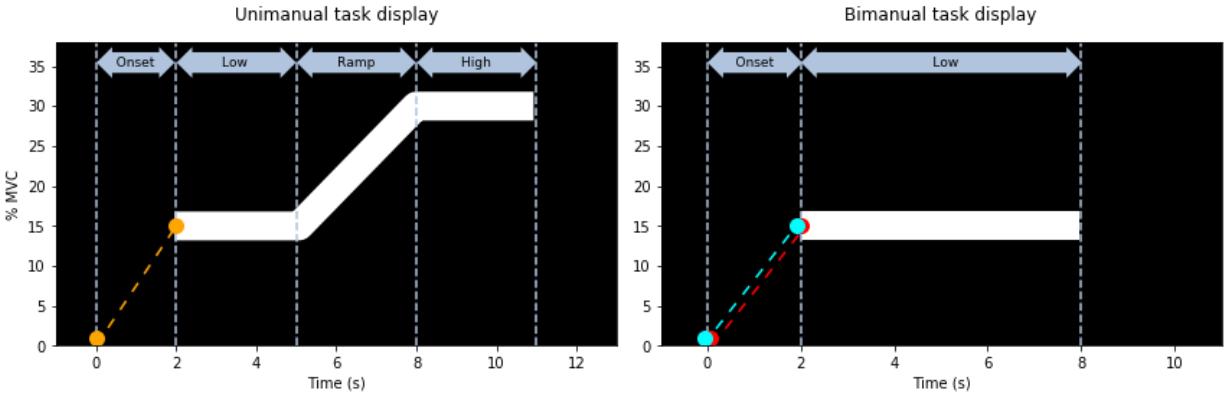

Fig.1: Task display. Left figure: Unimanual task. The task is subdivived into different phases: Onset (trial onset), Low (isometric contraction at 15% MVC), Ramp (force increase) and High (isometric contraction at 30% MVC). The orange dot appears at task onset and represents the force applied by the participant.Right figure: Bimanual task. The task is also subdivided into 2 phases as described.The blue and red dot represent each hand's applied force.

Motor task 1 - unimanual

At the onset of the trial, an orange circle appeared on the screen, which indicated the force output. Participants had 2 seconds to squeeze the gripper until it reaches 15% of their MVC. They then had to keep their force constant for 3 seconds, delimited by the "Low" part in Figure 1. Over the next 3 seconds, participants had to ramp up their force linearly to 30% of their MVC. This phase is labelled as "Ramp" in Figure 1. Then, participants held the 30% MVC constant for another 3 seconds, labelled as "High" in Figure 1. The trial then restarts for a total of 50 trials. A single trial lasted 11 seconds. The unimanual task had a total duration of approximately 13 minutes.

Motor task 2 – bimanual

At the onset of the trial, two circles (blue and red) appeared on the screen. Each color represented the force output of one hand. Participants had 2 seconds to squeeze both grippers until they both reach 15% of their respective MVCs ("Onset" on Figure 1). They then had to keep their force constant for 6 seconds at 15% MVC ("Low" on Figure 1). A single trial lasted 8 seconds. The bimanual task had a total duration of approximately 10 minutes.

For both tasks, participants had an inter-trial rest period which jittered between 3 to 5 seconds. During this time, participants looked at a white cross displayed on the screen.

DATA ACQUISITION & PREPROCESSING

Behavioural handgrip acquisition

Two plastic, non-magnetic, fiber optic hand grippers were used as part of this study (*Current Designs Inc, USA*), allowing a linear measurement of force output based on the pressure applied. The grippers were connected to a 932 interface through a 3m long fiber pigtailed connector. This interface received hand gripper signals located inside the MEG suite and converted them into electrical signals that were then transferred to a computer.

Structural MRI acquisition & preprocessing

A structural scan was acquired a for each participant. T1-weighted MRI images were acquired on a 3T MRI scanner (Siemens Prisma; TR = 2300 m s; TE = 2.32 m s; field of view = 240 mm; voxel size = 0.9 × 0.9 × 0.9 mm). This scan was used for co-registration of anatomical references between the MEG and MRI systems. This was done by defining the head surface points and the positions of the nasion, left and right pre-auricular points.

Neuroimaging data acquisition & preprocessing

Data acquisition:

A 275-channel CTF whole-head system was used to acquire MEG recordings. An empty room recording was collected each session before recording subject MEG data. These recordings are used in subsequent offline analyses for environmental noise correction. Participants changed into non-magnetic clothes prior to going in the MEG suite. They were seated with arms resting on the armchair. Bipolar electrocardiogram (ECG) was acquired to correct for cardiac artifacts, and vertical bipolar electrooculogram (EOG) for eye movements. Signals were amplified and collected at a sampling rate of 2400 Hz.

Data preprocessing:

Motor task data were epoched from -2.5 to +14s in the unimanual task and from -2.5 to +11s in the bimanual task. For each epoch, time 0 indicates the start of the trial where visual cue is provided (Fig. 1, *Onset* marks the beginning of the trial). MEG raw data were processed offline using the open-source software Brainstorm (Tadel et al., 2011). Notch filters were applied to

remove artifacts caused by power lines around 60Hz and harmonics (120Hz, 180Hz, etc.). MEG signals were downsampled to 400 Hz. Correction for cardiac and eye movement artifacts were done based on the ECG and EOG signals using signal-space projection (SSP). Independent component analysis (ICA) was used to detect and remove artifacts caused by external magnetic fields. Motion artifacts or epochs where the participant's head moved more than 5mm were discarded from the subsequent analyses.

DATA ANALYSIS & STATISTICS

For behavioural assessments (9HPT, BBT, PPT, HGS, MMSE) and comparisons between group counts (epochs kept in resting state and motor tasks), Wilcoxon rank-sum tests were used to determine differences between younger and older adults.

Behavioral handgrip analysis

The applied force was recorded for offline analysis in both the *x* and *y* positions. The main measure of motor performance in this study was *task accuracy*: this was quantified as the root mean squared error (RMSE) between the position of the point on the screen and the middle of the target ramp on the y axis. For each subject, RMSE was calculated for each time point and averaged over time and trials. When trials exceeded 3 standard deviations, they were considered outliers and therefore were removed for the computation of task accuracy.

MEG source imaging

MEG data was projected to source space. The overlapping spheres method was used to obtain lead fields of the head model, by computing locally fitted spheres under each sensor. (Huang et al., 1999). 15,000 current dipoles were estimated across the cortical surface, where dipoles are oriented perpendicularly to the cortical envelope. Then, source modeling was performed using a modified linearly constrained minimum variance (LCMV) beamformer method (Van Veen et al., 1997). This method required a data covariance matrix as well as a noise covariance matrix: the noise covariance matrix was estimated from the 2-min empty room recordings collected prior to every session, and the data covariance matrix was estimated from the epoched MEG recordings. Data covariance matrix was stabilized using the median eigenvalue parameter implemented in Brainstorm.

M1 hand region localization from time-frequency maps

Time-frequency (TF) maps were computed in order to locate the region within M1 that was most active during the motor tasks. From previous work (Xifra-Porxas et al., 2019), we showed that MRBD is the strongest when subjects increased their force: from rest to onset or from 15% to 30% of their MVC.

TF maps were computed across the whole brain in source space in the beta rhythm (15-29Hz) using Morlet wavelets (central frequency = 1Hz, time resolution (FWHM) = 3 sec) and averaged across trials for each subject. The evoked response was removed from each trial before computing the TF maps (Tadel et al., 2011). Then, spatial smoothing of 5mm was applied. The resulting TF maps were averaged in time during RAMP in the unimanual task [5, 8] sec of trial and during ONSET in the bimanual tasks [0, 2] sec of trial, where maximum MRBD was expected. Relative beta power was then calculated from the formula:

$$ERSD(P(t)) = \frac{P(t) - \mu}{\mu} * 100$$

where *P(t)* is the absolute power at time *t* on each vertex and μ is the mean over baseline (B). *B* was defined as the mean power during the inter-trial phase, i.e., in the time prior to onset [-1, 0] sec.

Using the resulting TF map, hand region in M1 was visually localized: the area within M1 that had the strongest MRBD was chosen. Approximately 20-30 vertices were expanded around the local maxima. We chose a small region on purpose since a larger area may include other body parts than the hand area which may affect phase-amplitude coupling results once averaged within the region.

To note: Due to strongest overall MRBD being present in other regions than M1 (e.g., OC, PC), the local maxima in M1 had to be localized visually. This prevented us from defining a clear threshold to select for maximally active regions in M1.

Local PAC

Time-resolved phase-amplitude coupling (tPAC) was computed for each trial in the selected region of M1 using the Brainstorm software (Samiee & Baillet, 2017). This method scans for the low φ_{f_φ} with the strongest coupling to f_A bursts.

Due to high computation demand and time constraints, we first ran a full tPAC analysis on a subset of subjects selected randomly (n=6). Spectral range of interest was defined as low-frequency beta band between 16-29 Hz for φ_{f_φ} and the range of high-frequency gamma band was divided into 20 centre frequencies linearly from 30-100 Hz. tPAC maps were averaged across trials and the comodulogram were extracted from these maps to find the main mode of coupling. The single-band analyses would then be performed with the main mode of coupling. However, in local tPAC (referred to as local PAC), we were unable to find a reliable main mode of coupling (Appendix II, Section I). Thus, we relied on the results from the inter-regional tPAC (referred to as irPAC) to identify the main mode of coupling and used those results to perform single band tPAC in local M1.

Initially, based on the duration of the state (active, resting), the necessity to resolve minimally two cycles of the slowest oscillation (16Hz) and the requirement for a better resolution for phase, we chose 250ms as the sliding time window over which tPAC was computed. However, due to computational requirements, we extended the time window to 500ms for unimanual tasks and 250ms for bimanual tasks. Thus, the epoch over which PAC was computed was defined as [-1.1, 11] sec, where 0 sec is the onset of the trial (Fig. 1). This time window represented the entirety of each trial. The same tPAC analysis was performed for bimanual tasks, where the time window was defined as [-1.1, 8] sec.

As strength of coupling resulting from the tPAC analysis yields an arbitrary number, surrogate data was generated in Brainstorm in order to build a null distribution for statistical analysis. A set of 250 surrogates were generated from the data. Then, PAC values were transformed to z-score values with respect to surrogate data. Thus, a large z-score would indicate stronger coupling. This analysis was performed separately on both the contralateral M1 (cM1) and the ipsilateral M1 (iM1), where cM1 is the contralateral cortex to the dominant hand.

Local PAC statistics

We used a two-sample t-test using the spm1d package in Python to evaluate the differences in local PAC between old and young adult at each time point (Pataky et al., 2016).

In order to determine differences across each phase of the motor task, data was grouped in 5 time periods over each trial (REST, ONSET, 15%MVC, RAMP, 30%MVC) for unimanual data and 3 time periods (REST, ONSET, 15%MVC) for bimanual data (Fig. 1). 2-way ANOVA was then computed to determine differences due to *age* and *task phase*. If the main results are significant, post-hoc Tukey's Honestly Significant Difference test (Tukey HSD) was used to determine where the differences were found.

Inter-regional PAC (irPAC)

We could not complete surrogate data analysis in irPAC domain as it was not implemented yet in Brainstorm; however, we decided to include the preliminary results due to the potential they show.

tPAC was also computed inter-regionally across both M1s. As there is no clear *a priori* in terms of directionality, each cortex was used as a driver network (where f_φ is measured) and the other as the driven network (where f_A is measured) to run two separate analyses. The driver cortex was thus defined to be either in iM1 or cM1. When driver is in iM1, we refer to this direction as $iM1_\varphi \rightarrow cM1_A$. In contrast, when the driver is in cM1, we refer to it as $cM1_\varphi \rightarrow iM1_A$. If the driver is in cM1, the f_φ is at one vertex in cM1 and is tested for significant coupling with the amplitude at each of the 20 center frequencies in the gamma band in iM1.

We ran full tPAC analyses on the same subset of 6 subjects to reduce computational load subsequently for inter-regional tPAC (irPAC). Main mode of coupling was extracted visually to run single band irPAC analysis. Thus, single band tPAC analysis was performed with beta and the defined ranges for gamma (low gamma: 40-55 Hz, high gamma: 65-95 Hz), since we found coupling at each of the two high frequency bands in the comodulogram (see Results: irPAC). The main beta frequency was found to be between 20-22 Hz. As there are no options to generate surrogate data for inter-regional tPAC in Brainstorm yet, we proceeded to statistical testing using the raw values from tPAC computation.

Interregional PAC statistics

We used a two-sample t-test using the spm1d package in Python to evaluate the differences in irPAC between old and young adult at each time point (Pataky et al., 2016).

In order to determine differences across phases of the motor tasks, data was grouped using the same period as described for local PAC statistics (5 for unimanual and 3 for bimanual task). Two-way ANOVA was then computed to determine differences due to *age* and *task phase*.

To determine whether there was a directionality effect as well, a two-way ANOVA was computed with *driver* and *age* in each respective f_A band, where *driver* refers to the cortex where f_φ is measured.

Associations between local PAC & motor performance

Pearson's correlation test was used to determine whether the subject's error on task performance and tPAC are **linearly** correlated with coupling value at each time point. Since error on the task was recorded at a higher sampling rate, the time series of task error was downsampled to match the sampling rate of tPAC outputs. Absolute task error was compared to tPAC value on a single time point in each trial.

For each trial and timepoint, the matching task error and tPAC value were correlated. In order to maximise the detection of an association between error on the task and PAC, only extreme values were used to establish a linear correlation. The larger and smaller 25% of the motor tasks' absolute errors and their corresponding local PAC values were used to calculate Pearson's correlation factor. The median 50% were not considered in the analysis.

CHAPTER III | RESULTS

BEHAVIOURAL ASSESSMENT

The results from the behavioural assessments have been reported in detail in a previous publication from our group (Xifra-Porxas et al., 2019). Briefly, significant differences between older and younger adults were found for both hands on the behavioural assessment scores for the 9HPT, BBT and PPT motor tests, where older adults performed significantly worse ($p < 0.01$).

MOTOR TASK PERFORMANCE

In the unimanual task, older and younger adults performed similarly and there were no significant differences in RMSE (unimanual: $t = 0.316$, p = 0.756, Fig. 2A).

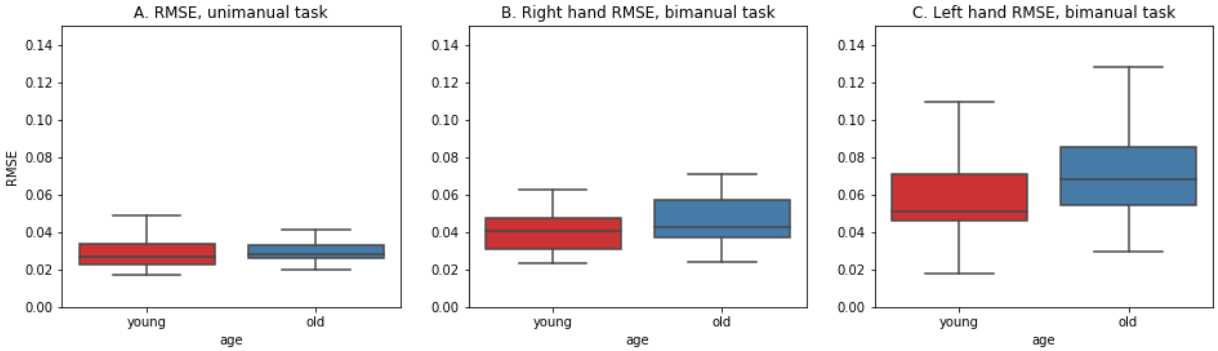

Fig.2: Comparison of the performance on the motor task between young and old adults. The differences between age groups were non-significant, with older adults generally making more errors than younger adults. For all the box plots in this study, the limits of the box shows the quartiles of the data and the whiskers show the rest of the distribution. Outliers are excluded, thus not shown.

No difference in performance was observed for the bimanual task either (Right hand: t = -0.978, p = 0.339, Fig. 2B; Left hand: t = -1.550, p = 0.136, Fig. 2C).

LOCAL PAC

Main modes of coupling

Full tPAC maps were performed for 6 subjects in cM1 (Appendix II, Section i). The comodulogram was extracted from these subjects and averaged across sources. Stronger coupling between 17-19Hz for f_φ and 45-55 & 70-80Hz were observed for f_A. However, these results may be due to edge effects seeing that only lower beta band shows any coupling. Thus, we relied on results from the full tPAC maps from inter-regional analyses to identify the main

modes of coupling (Appendix II, section i). The multiple band full irPAC analyses showed that the beta band frequency with the strongest coupling to gamma amplitude lies between 20-23 Hz. The comodulogram from irPAC analysis indicated two main modes of coupling with the gamma band which were used for the single band local PAC analysis as well (further details in *Results: irPAC*).

Unimanual task

Contralateral M1 (cM1)

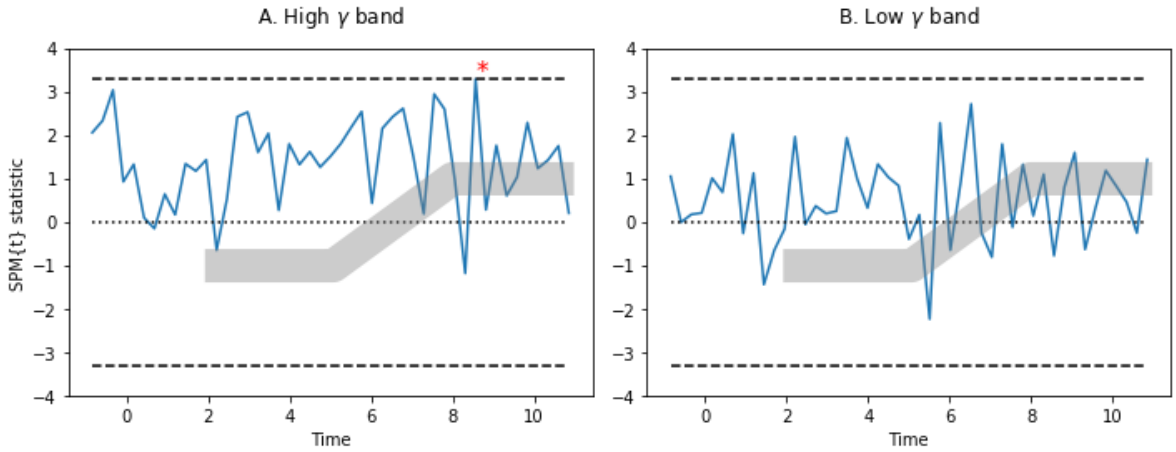

Fig. 3: SPM two-sample t-test results in cM1 showing the t-statistic on the y-axis, which represents the difference in coupling strength between old and young adults at each point during the motor task. SPM{t} = 0 indicates no difference, whereas upper and lower dashed lines indicate the t-value at which p=0.05. Points between these dashed lines are not significantly different.
In the left figure, the red star (*) indicates one point in time where the difference between old and young adults was significantly different (p=0.05). This difference was found in the 30% MVC phase. The transparent grey bar on each figure represent the phases of the unimanual motor task.

SPM analyses revealed very noisy data with no clear temporal pattern where the two groups differed. No significant difference between age groups were found for coupling with the low gamma band ($p > 0.05$ at each time point evaluated), but a significant difference between age groups was found for beta-high gamma PAC at a single time point ($p = 0.05$, Fig. 3A: the red asterisk indicates the only significant time point).

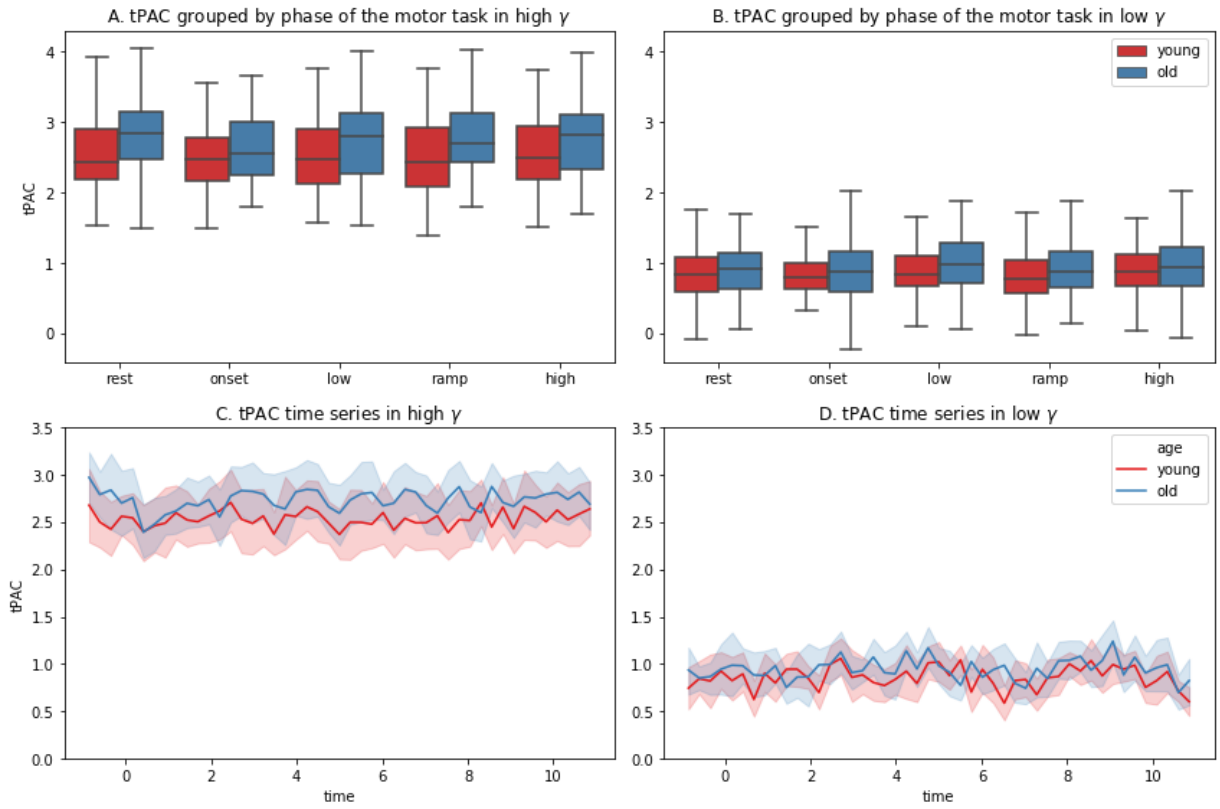

Fig. 4: Local tPAC in cM1. Upper graphs represent tPAC values grouped in phases of the task, while lower graphs represent time series of the z-scored tPAC. Red represents young adults and blue represents old adults.

In beta-high gamma PAC, a two-way ANOVA showed no effect of task phase on PAC (p = 0.267) but a main effect of age (p < 0.001, Fig. 4A, C). The interaction between task phase and age was not significant (p = 0.545), suggesting that older adults have generally higher coupling but is not changing throughout the task.

In the coupling with the low gamma band, the two-way ANOVA showed a main effect of task phase (p = 0.037) but did not survive Tukey multiple comparisons (low vs ramp: p = 0.0594, largest mean difference = -0.090; Fig. 4B, D). Age main effects were significant as well (p < 0.001, Fig. 4B, D). The interaction, however, was not significant (p = 0.918), supporting the results from the SPM two-sample t-test null results.

Ipsilateral M1 (iM1)

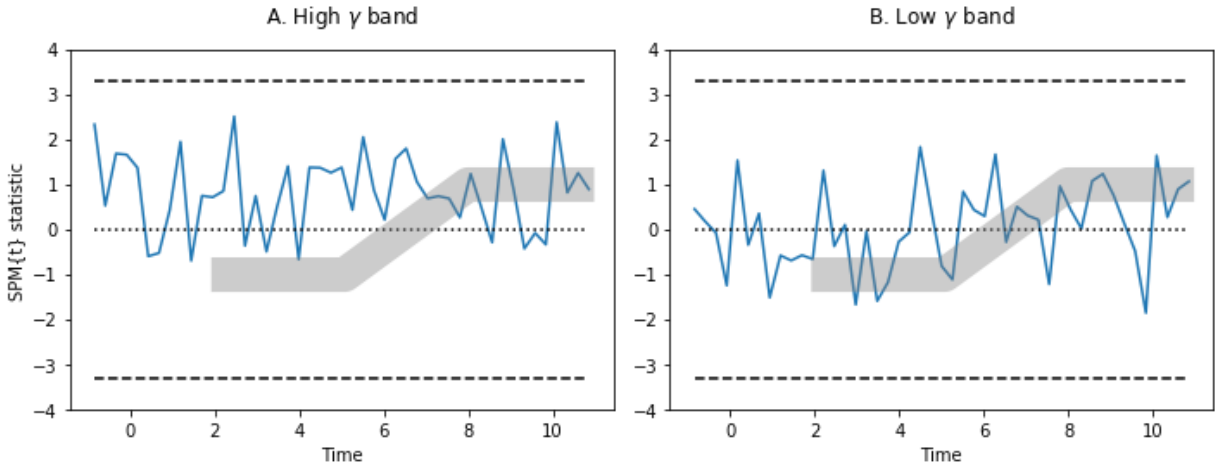

Fig. 5: SPM results in iM1. No significant differences between old and young adults were found at any time point in both high and low γ bands ($p > 0.05$). The grey bars represent the phase of the unimanual motor task.

Two-sample t-tests using SPM revealed no clear temporal pattern of difference between the two groups. No significant difference between age groups were found in the beta band coupling with the low gamma one ($p > 0.05$ for all time points, Fig. 5A), nor with the high gamma band ($p > 0.05$ for all time points, Fig. 5B).

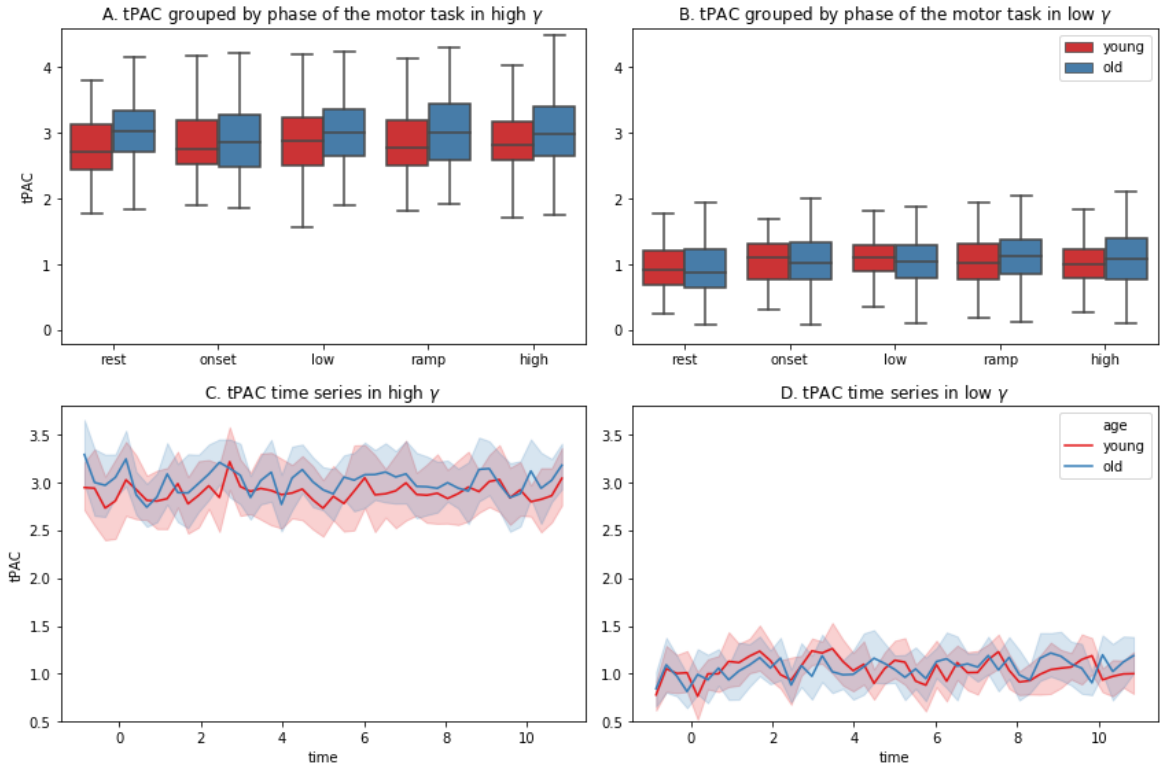

Fig. 6: Local tPAC in iM1. Upper graphs represent tPAC values grouped in phases of the task, while lower graphs represent time series of the z-scored tPAC. Red represents young adults and blue represents old adults.

In beta-high gamma coupling, a two-way ANOVA indicated no effect of task phase on tPAC ($p = 0.814$) but a main effect of age ($p < 0.001$, Fig. 6A, C). The interaction was not significant ($p = 0.860$), supporting SPM's null results in the t-tests.

In beta-low gamma coupling, the two-way ANOVA indicated no main effect of task phase ($p = 0.097$). Age main effects were not significant either ($p = 0.701$, Fig. 6B, D), as well as the interaction between task phase and age ($p = 0.464$).

Bimanual task

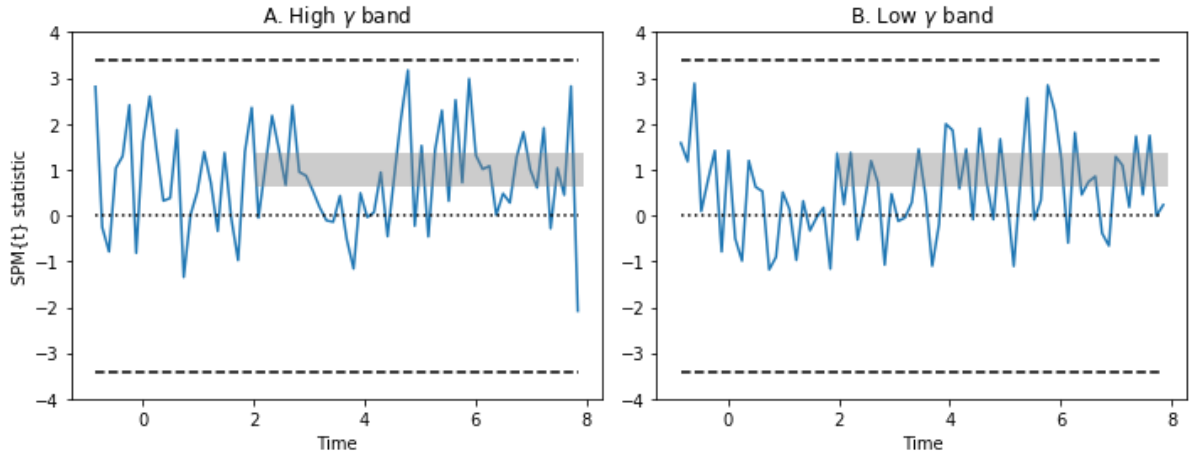

Fig. 7: SPM results in bilateral M1 during bimanual task. No significant differences between age groups were found at any time point in both high and low γ bands (p>0.05). The grey bars represent the phase of the bimanual motor task.

SPM's two-sample t-tests revealed similarly noisy data in the differences between old and young adults across time. No significant differences were observed between groups across task phases in either beta-low gamma or beta-high gamma PAC ($p > 0.05$ for all time points in both frequencies, Fig. 7A, B).

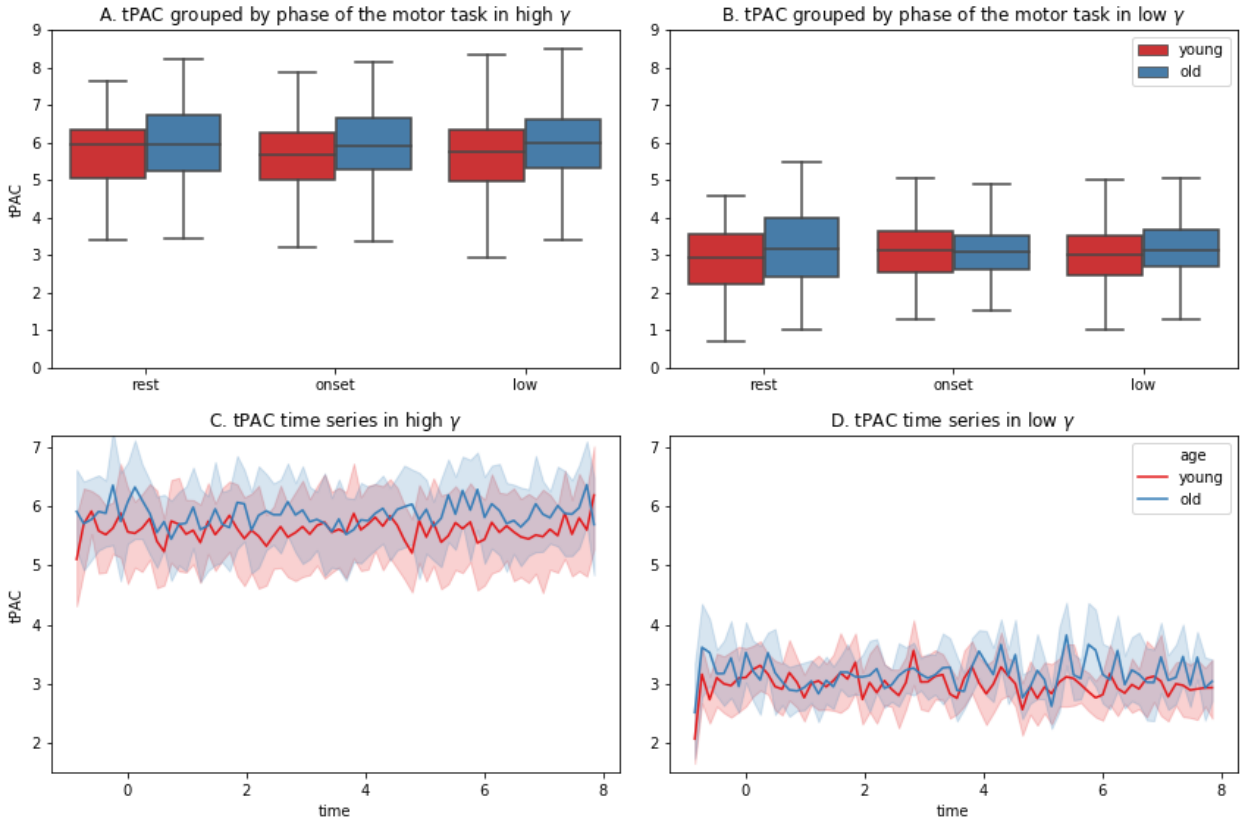

Fig. 8: tPAC during bimanual task in bilateral M1.

In beta coupling with the high gamma band, using a two-way ANOVA, no significant main effect of task phase ($p = 0.901$) but a significant main effect of age ($p < 0.001$) was observed (Fig. 8A, C). However, the interaction was not significant ($p = 0.990$).

In beta coupling with the low gamma band, there was no main effect of task phase ($p = 0.773$) but a main effect of age ($p < 0.001$, Fig. 8, right panels). The interaction was not significant ($p = 0.131$).

INTER-REGIONAL PAC (irPAC)

It should be reminded that for irPAC, no surrogate data was generated. The coupling values provided in this section represent the raw values obtained from the computation of tPAC.

Main modes of coupling

Based on the results obtained from the multiple band inter-regional tPAC analysis, two main modes of coupling were identified (Appendix II, **Section ii & iii**).

The comodulograms of full inter-regional tPAC when $cM1_{\varphi} \rightarrow iM1_{A}$ can be found in **Section ii**, where beta phase in cM1 modulates gamma amplitude in iM1. Beta band was identified to be between 20-23Hz. In this direction, two main frequencies f_A could be identified: between 40-60 Hz and above 70 Hz. In the other case, when $iM1_{\varphi} \rightarrow cM1_{A}$, the main $f_A$seems to be broadband above 65 Hz and is shown in **Section iii**. Hence, the following paragraphs show the irPAC results in each direction.

Unimanual task: $cM1_{\varphi} \rightarrow iM1_{A}$

In this section, we considered the coupling of the beta phase in cM1 with the gamma amplitude in iM1.

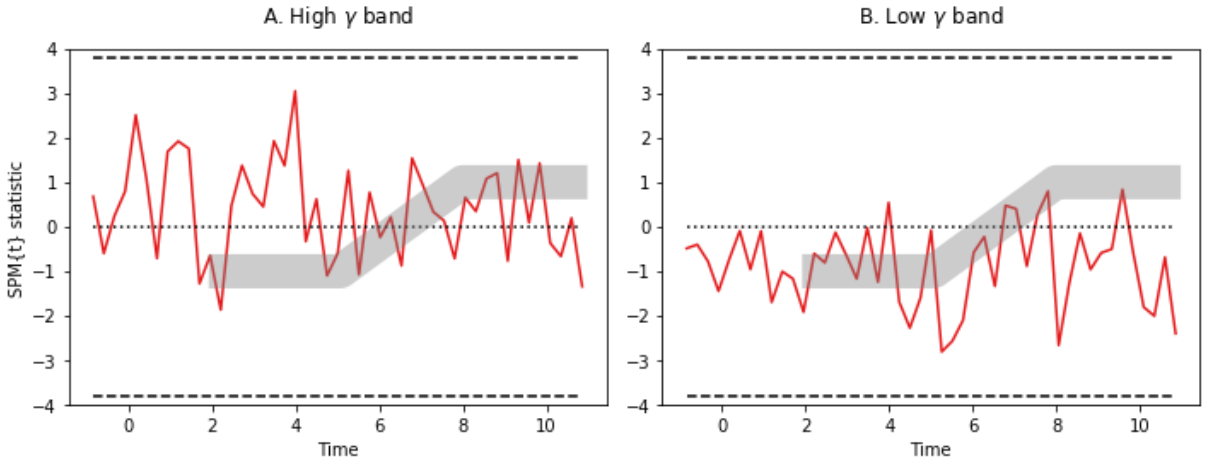

Fig. 9: SPM results from irPAC with seed in cM1. There were no significant differences between age groups at any time point (p > 0.05).

The SPM analysis showed non-significant differences between old and young in irPAC values for both high ($p > 0.05$ for all time points, Fig.9A) and low gamma bands ($p > 0.05$ for all time points, Fig. 9B).

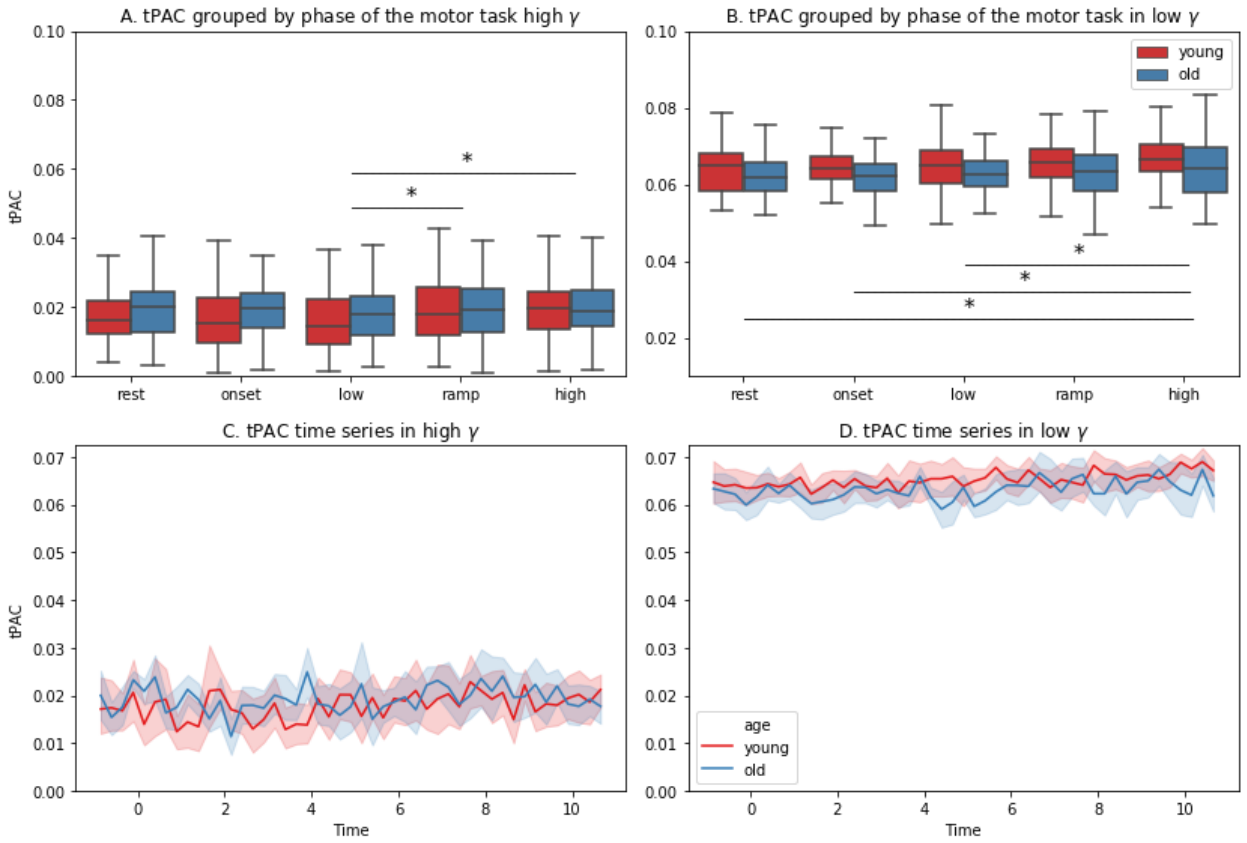

Fig. 10: Inter-regional tPAC where beta phase in cM1 (seed in cM1) modulates gamma amplitude in iM1.

For the beta coupling with the high gamma band, the two-way ANOVA revealed a significant difference between phases of the motor task (p = 0.010) and between age groups (p = 0.009) with older adults having stronger coupling (Fig. 10A, C). However, the interaction term age*task phase was not significant (p = 0.911). Post-hoc Tukey test showed that 1) the 15%MVC and the RAMP phases were significantly different from each other (p = 0.002), and 2) the 15%MVC and the 30%MVC phases of the unimanual task were significantly different (p = 0.021).

For the beta coupling with the low gamma band, the two-way ANOVA revealed a significant difference between phases of the motor task (p < 0.001) and age groups (p < 0.001) as well, while the interaction remains non-significant (p = 0.985, Fig. 10B, D). Post-hoc Tukey tests revealed significant differences between the following pairwise comparisons between phases of the motor task: 1) REST vs 30%MVC (p = 0.008), 2) ONSET vs 30%MVC (p = 0.001), 3) 15%MVC vs 30%MVC (p = 0.002).

Unimanual task: $iM1_{\varphi} \rightarrow cM1_{A}$

In this section, we considered the coupling of beta phase in iM1 with gamma amplitude in cM1.

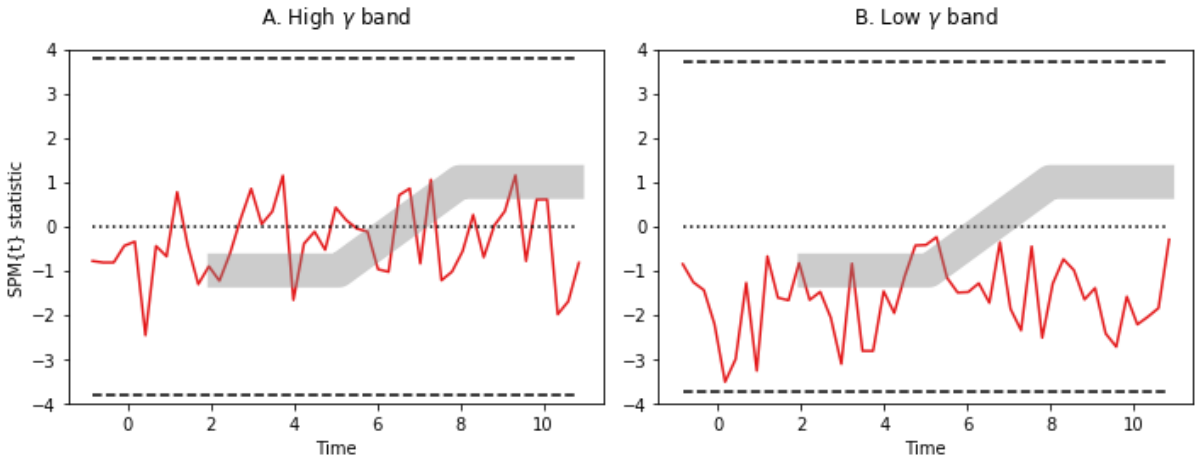

Fig. 11: SPM results from irPAC with seed in iM1. There were no significant differences between age groups at any time point (p > 0.05).

There were no significant differences between old and young adults across all time points in both the beta-high gamma and beta-low gamma irPAC ($p > 0.05$ for all time points in both gamma frequencies, Fig. 11).

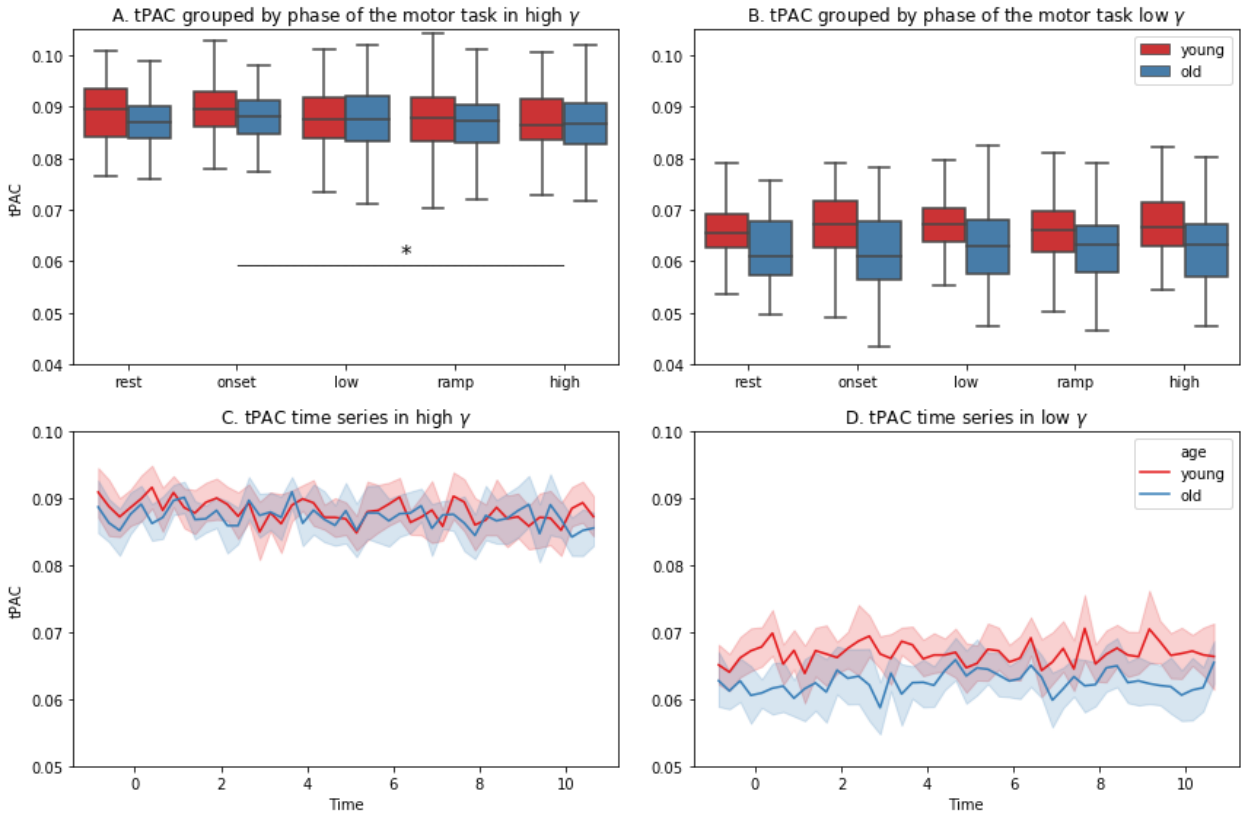

Fig. 12: Inter-regional tPAC where beta phase in iM1 (seed in iM1) modulates gamma amplitude in cM1.

For the beta coupling with the high gamma band, the two-way ANOVA revealed a significant difference between phases of the motor task (p = 0.035) and age groups (p = 0.019), with younger adults showing stronger irPAC. However, the interaction term was not significant (p = 0.727, Fig. 12A, C). Post-hoc Tukey test revealed that a significant difference between ONSET and 30%MVC phases of the unimanual task in the high gamma band (p = 0.018, Fig. 12A).

For the beta coupling with the low gamma band, the two-way ANOVA revealed no differences in coupling throughout different phases of the motor task (p = 0.407). However, the difference between age groups was significant (p < 0.001, Fig. 12B, D), where younger adults had stronger irPAC. The interaction was non-significant (p = 0.782).

Comparing directionality

In this section, we compared inter-regional coupling strength in both directions: beta phase in cM1 to gamma amplitude in iM1 ($cM1_{\varphi} \rightarrow iM1_{A}$) and vice-versa ($iM1_{\varphi} \rightarrow cM1_{A}$).

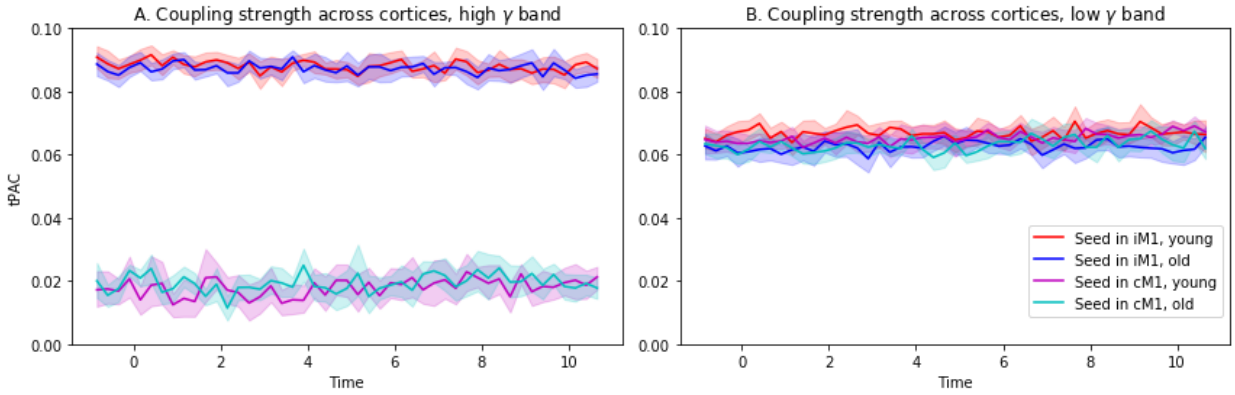

Fig. 13: Comparison of the coupling strength between cortices. In the left panel in the high gamma band, there is a noticeable difference in coupling strength: Beta phase in iM1 is coupled to γ amplitude in cM1 more strongly than beta phase in cM1 is coupled to γ amplitude in iM1.

Coupling in $iM1_{\varphi} \rightarrow cM1_{A}$ was stronger than in $cM1_{\varphi} \rightarrow iM1_{A}$. In other words, beta phase in iM1 was coupled to gamma amplitude in cM1 more strongly than it was for the reverse direction (Fig. 13A). In the beta-high gamma coupling, the two-way ANOVA revealed a significant effect of directionality (seed cortex, $p < 0.001$) but no significant effect of age ($p = 0.402$). The interaction term between seed and age (seed*age) was also significant ($p = 0.001$), suggesting that PAC directionality changed due to age. Beta phase in iM1 was more efficient at driving gamma amplitude in cM1. For the coupling in $iM1_{\varphi} \rightarrow cM1_{A}$ younger adults had slightly more coupling than older adults. The order was reversed for coupling in $cM1_{\varphi} \rightarrow iM1_{A}$: when looking at the strength of coupling from beta phase in cM1 to gamma amplitude in iM1, older adults had stronger coupling.

For the beta-low gamma coupling, the two-way ANOVA revealed no significant difference in directionality ($p = 0.107$) but a significant effect of age ($p < 0.001$) and of the seed*age interaction term ($p < 0.001$). Overall, younger adults showed more coupling than older ones in both directions; however, the effect was smaller when the driver was in cM1.

ASSOCIATIONS BETWEEN LOCAL PAC & MOTOR PERFORMANCE

We tested the linear association between local PAC strength and error on motor performance using the smallest and largest 25% of the absolute errors. Overall, younger and older adults showed different trends in terms of this association.

Unimanual task

cM1

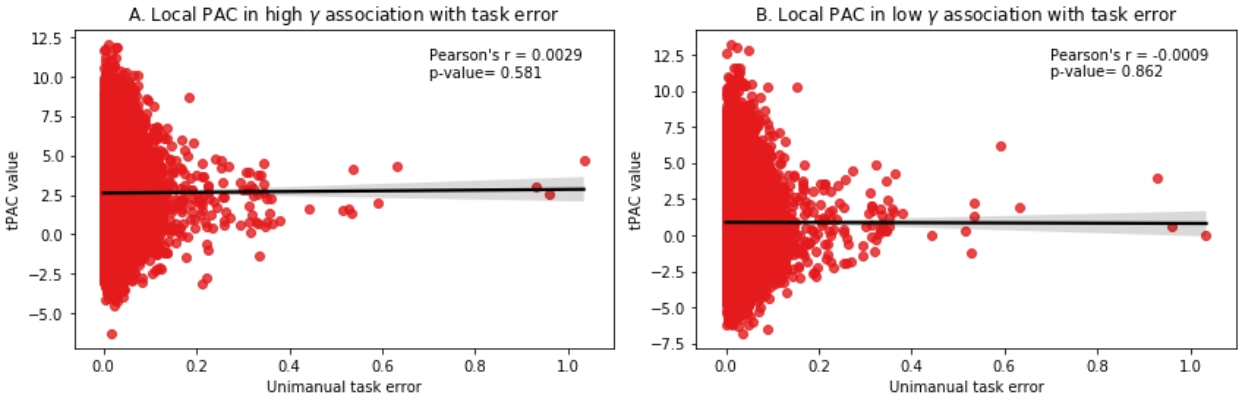

Fig. 14: Association between local PAC in cM1 and unimanual task error.

In both frequency bands for amplitude, error was not significantly correlated with strength of coupling in cM1 (beta-high gamma PAC in Fig. 14A: r = 0.003, p = 0.581; beta-low gamma PAC in Fig. 14B: r = -0.001, p = 0.862).

iM1

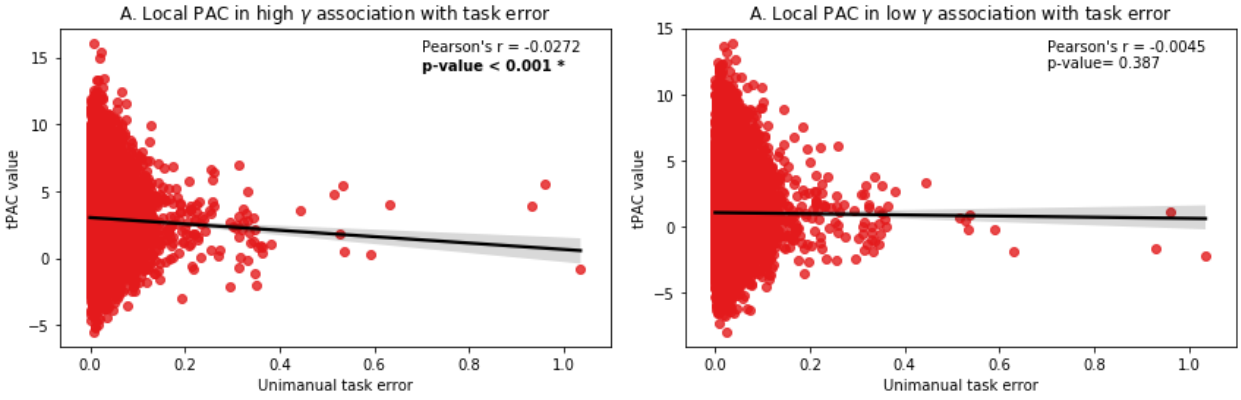

Fig. 15: Association between local PAC in iM1 and unimanual task error.

In beta coupling with the high gamma bands, there was a weak but significant association between error and local PAC in iM1 (r = -0.027, p < 0.001, Fig. 15A). There was no significant association in beta coupling with the low gamma bands (r = -0.005, p = 0.387, Fig. 15B).

Bimanual task

In the bimanual task, associations were weak but significant in both frequency bands for amplitude (beta-high gamma PAC in Fig. 16A: $r = 0.022$, $p < 0.001$; beta-low gamma PAC in Fig. 16B: $r = 0.01$, $p = 0.039$).

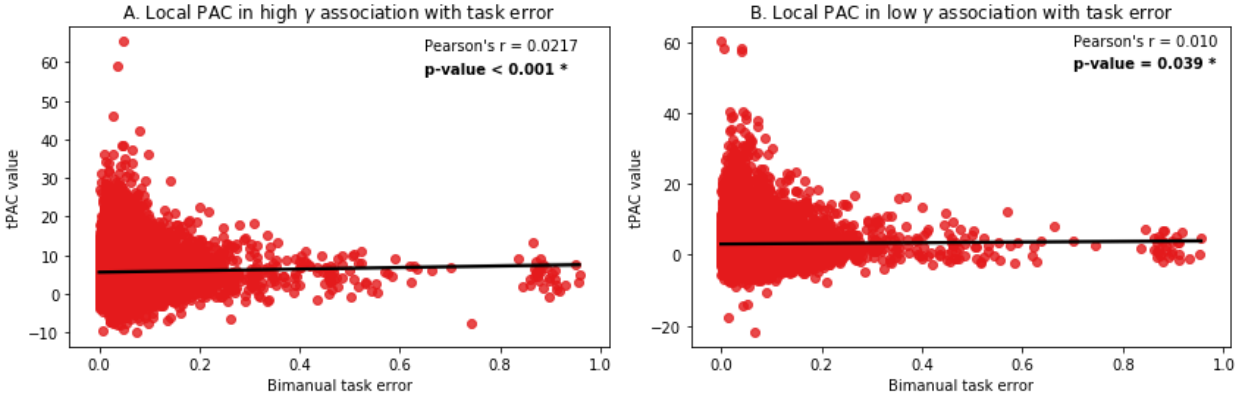

Fig. 16: Association between local PAC in bilateral M1 and bimanual task error averaged between hands.

CHAPTER IV | DISCUSSION

In this study, we evaluated the temporal changes in local and irPAC in bilateral M1s during the different phases of two visuomotor handgrip tasks, as well as the changes in PAC related to aging.

Concerning our initial hypotheses, we saw no consistent changes in local PAC across the phases of the motor tasks but there were changes in irPAC across the phases of the motor task. For the $cM1_{\varphi} \rightarrow iM1_{A}$ irPAC, production of larger force was associated with consistently stronger coupling with both the high and low gamma bands. For the $iM1_{\varphi} \rightarrow cM1_{A}$ irPAC, production of larger force was associated with the weakest coupling only with the high gamma band; in the low gamma band, irPAC did not change across phases of the motor task. Overall, older adults had stronger local PAC, which was especially visible in the high gamma bands in both uni- and bi-manual tasks, but weaker irPAC compared to their younger counterparts except for the $cM1_{\varphi} \rightarrow iM1_{A}$ direction, where older adults showed stronger coupling. The weaker irPAC in older adults was especially visible with the low gamma band There were some significant correlations between local PAC and motor task accuracy, but the effect size was very small.

In the following sections, the inferences from these results in the context of understanding the interactions between beta-gamma bands in bilateral M1 during motor tasks are discussed in greater details.

MOTOR PERFORMANCE

Older and younger adults performed similarly well on the two motor tasks. As described in a previously published report (Xifra-Porxas et al., 2019), this might be due to the simplicity of the task, which did not involve learning. During data collection, participants reached a plateau in their motor performance quickly, after only a few trials, after which the performance stabilized for the remaining trials. The required grip force for each task was normalized to each subject's individual MVC such that the perceived effort would be the same and the differences between old and young adults would be purely due to age and not due to increased effort or difficulty (Aine et al., 2006).

Other studies have reported a decrease in fine and gross motor measures in older adults as the task difficulty increases (Maes et al., 2017; Seidler et al., 2010). It has also been shown that during bimanual tasks, older adults have reduced accuracy, larger variability and longer reaction times (Krehbiel et al., 2017). This suggests that the use of a more difficult task would have been more optimal to differentiate older and younger adults in terms of motor performance and to relate neurophysiological findings to their performance.

However, in terms of behavioural scores, older adults had significantly lower performance on the 9HPT, BBT and PPT (Xifra-Porxas et al., 2019). This result supports the idea that age had am impact in terms of motor performance in our cohort of older adults, but the motor task used in this study was not difficult enough to reveal motor performance differences between age groups.

LOCAL PAC

All data were z-scored before performing statistical analyses on them to control for false positives and provide statistical reference for our results (Gohel et al., 2016).

For the local PAC analysis, we found from the full tPAC computation that the main modes of coupling were between 17-19 Hz for the beta band with broad band gamma coupling across 30-100 Hz. These results led us to revaluate the validity of these findings and consider them to be due to edge effects, seeing that only lower beta band shows any coupling with a broad-band gamma spanning the entire testing range. The main modes of coupling chosen for local PAC relied exclusively on the frequencies found during the inter-regional full tPAC computation. This could explain the weak results we find in terms of local PAC.

Unimanual tasks

Older adults had significantly stronger coupling between beta and **high gamma bands** in both cM1 and iM1 across the duration of the trial. This is in line with the increased activation observed in bilateral M1 in older adults obtained from fMRI studies (Naccarato et al., 2006) where older adults showed an increase activation in bilateral M1s during a finger tapping task in comparison to younger adults. The precise meaning of this increased coupling in terms of physiological role remains unknown as few studies have looked at PAC during movement

production. It has been suggested that PAC represent the transient openings for information flow by facilitating the synchronization of higher frequencies (Fries, 2005; Gonzalez et al., 2020; Siegel et al., 2012). Beta-high gamma PAC was present in both old and young adults, but the coupling strength was visibly and significantly stronger in older adults. This could mean that the stronger local PAC in both M1s in older adults represent a more efficient local processing, which in turns may reflect a potentially compensatory brain mechanism to compensate for stronger beta power or a reduced gamma power. Another possibility is that the stronger local PAC in older adults represents an excessive phase-locking of gamma amplitude to the beta frequency, which implies that the pro-kinetic gamma rhythm is hindered by locking its amplitude to beta phase, preventing it from fulfilling its functional role in M1 (De Hemptinne et al., 2013; van Wijk et al., 2016). Our results support the latter view since there was a more pronounced coupling in iM1 (the non-moving cortex) compared to cM1 (the moving cortex) (**Appendix III, notebook 2**). Thus, the **increased beta-gamma PAC** observed in older adults may not be beneficial to movement production.

A limited number of studies have looked at beta-gamma PAC in the motor domain and these studies have reported diverging results. In children with autistic spectrum disorder, PAC in iM1 was reduced during a button-press task compared to healthy age-matched controls (An et al., 2021). This is interesting in the context of our study because the children with autism showed decreased MRGS and increased pre-movement beta ERD, which is similar to the brain oscillatory patterns reported in aging (Bardouille & Bailey, 2019). In the large-scale study by Bardouille & Bailey, the authors showed an age-related decrease in gamma burst amplitude but no change in frequency (Bardouille & Bailey, 2019). Despite the similarities regarding beta and gamma band changes between the children with autism and our results (An et al., 2021), we found that PAC in older adults was stronger compared to young adults, whereas autistic children showed reduced PAC compared to age-matched controls. This suggests that PAC relies on an independent, separate brain mechanism and is not a simple representation of movement-related beta and gamma power changes.

Beta-gamma PAC has been most studied is the Parkinson's Disease (PD) population, where it was shown to be stronger in the subthalamic nucleus (STN) (van Wijk et al., 2016) as well as in M1 (De Hemptinne et al., 2013). There was also increased PAC between the STN and

M1, which was linked to impaired motor performance (De Hemptinne et al., 2013; van Wijk et al., 2016). It was postulated that this excessive coupling may lead to dysregulation of motor processes via phase-locking of gamma oscillations. In a subsequent study from this group, (Cole et al., 2016), it was pointed that a non-sinusoidal beta waveform can create false indices of PAC. However, neuronal spikes in the STN were still found to be coupled to low frequency phases in M1 (Shimamoto et al., 2013) suggesting that the beta-gamma interactions are valid and thus important for movement production. In order to validate our PAC results, we considered the recommendations of Jensen et al., (2016), who proposed the following measures to distinguish valid from spurious PAC (Jensen et al., 2016): 1) use single neuron recordings when looking at gamma oscillations when possible, 2) evaluate whether irPAC is stronger than local PAC, and 3) evaluate if coupling strength increases when low frequency power decreases. We have considered the last two in our discussion.

In the **beta-low gamma coupling**, older adults had significantly stronger local PAC in cM1 but not in iM1. In comparison to beta-high gamma PAC, beta-low gamma PAC was weaker in both cortices, indicating that this local PAC may not have a significant role in movement directly. Although alpha-low gamma PAC reduction was associated with better implicit visuomotor learning (Tzvi et al., 2016), the role of beta-low gamma PAC remains unknown in the motor domain.

Low and high gamma bands have been shown to have clearly separate roles in motor processing. High gamma oscillations in the motor cortices have been linked to motor execution and learning, and MRGS is seen in the high gamma bands, where it is stronger in the first moments of a movement (Muthukumaraswamy, 2010). Transcranial alternating current stimulation (tACS) studies using stimulation at 70Hz or higher have shown that increasing high gamma oscillations improve motor performance, motor learning and reduces inhibition (Joundi et al., 2012; Moisa et al., 2016; Nowak et al., 2017; Santarnecchi et al., 2017; Sugata et al., 2018). These studies point to a pro-kinetic role of high gamma in movement production and motor processes. There is less evidence for the role of low gamma oscillations in movement, but the existing literature on this topic points toward differential roles played by low and high gamma bands in M1. For example, low gamma tACS (40 Hz used) was shown to worsen motor performance (Giustiniani et al., 2019). In another study,

PAC between alpha and low-gamma was associated with implicit visuomotor sequency learning (Tzvi et al., 2016). More specifically, a **reduced coupling** in these frequencies involving the parietal and frontal cortices was associated with better learning. The authors speculated that this coupling was not only related to motor processes, but also to the mapping of visual to motor output, pointing to a transitional role of low gamma oscillations in the motor cortices to promote the transfer of visual information. Furthermore, another study showed that cortico-muscular coherence shifts from the beta band to the low-gamma (or high-beta) band when transitioning from sustained to dynamic contraction (Omlor et al., 2007). There was an increase in cortical gamma power during dynamic contraction, although the effect did not reach significance. Nonetheless, these studies point to a transitional role from sensory to motor maps for low gamma oscillations in the motor cortices. In our study, beta-low gamma coupling was weaker than beta-high gamma coupling, suggesting that the beta-low gamma is not directly involved in motor performance, in line with the proposed transitional role of low-gamma (Omlor et al., 2007; Tzvi et al., 2016)

We found significant differences in PAC throughout the different phases of the task for the low gamma band only, but they did not survive multiple comparisons. The literature shows that MRGS is seen only in the early trials of a motor task and mostly in the high gamma bands (Muthukumaraswamy, 2010), while MRBD seems to last throughout the entire duration of the motor task (Xifra-Porxas et al., 2019). However, the PAC temporal patterns differed from both MRGS's and MRBD's, suggesting distinct brain mechanisms for PAC, which do not have the same origins as MRBD or MRGS. The two age groups had similar temporal patterns in terms of PAC strength throughout the task. We observed only one significant time during the 30%MVC phase for beta-high gamma PAC in cM1 where older adults had stronger coupling than younger adults. As the coupling magnitude is highly variable across the phases of the task and between groups, this result could be considered being due to chance.

Bimanual tasks

As for the bimanual task, older adults showed significantly more coupling than younger adults in bilateral M1s, and the difference was more apparent in the beta-high gamma coupling. We observed no difference in coupling strength between the different phases of the motor task,

suggesting no relationship between movement phases and PAC. Statistically, the z-scored PAC values from the bimanual task were higher than in the unimanual task, suggesting that bimanual tasks require stronger coupling within M1s than unimanual ones. This is consistent with previous findings that compared uni- and bi-manual tasks and where bimanual tasks were shown to require more brain resources than unimanual ones (Maes et al., 2017).

INTER-REGIONAL PAC

Raw values from the computation were used without z-scoring them thus the results provided in this section are preliminary. Without z-scoring, we cannot interpret the statistical significance of our findings. Although we can still compare both groups, the significance of the coupling could not be investigated. Hence, irPAC results are preliminary. In irPAC, we considered the coupling between M1s throughout the unimanual task.

When the driver cortex is cM1: $\boldsymbol{cM1_{\varphi} \rightarrow iM1_{A}}$

We observed irPAC in the $cM1_{\varphi} \rightarrow iM1_{A}$ direction, where the beta phase in cM1 (the moving cortex) was coupled to gamma amplitude in iM1 (non-moving cortex).

In the **beta-high gamma coupling**, we observed stronger irPAC in older adults, but it remains unclear whether this is related to increased activation in bilateral M1. fMRI studies have reported an increase in bilateral M1 activation and a reduced lateralization in older adults compared to younger adults during unimanual hand motor tasks (Naccarato et al., 2006; Talelli et al., 2008). This was argued to be due to a decrease in inter-hemispheric inhibition and overall increase in iM1 activity (Naccarato et al., 2006; Talelli et al., 2008). This change in bilateral M1 activation may reflect the stronger irPAC we observed in older adults, where the increase in coupling could represent a compensation mechanism associated with a decrease in inter-hemispheric inhibition. This suggests that older adults might have a more pronounced beta inhibition of iM1 via phase-locking instead of inhibition via the reciprocal connections between M1s. This communication by synchronization instead of direct synaptic communication has been proposed as a mechanism for brain-wide integration of information (Fries, 2005, 2015).

Older and younger adults had similar patterns of irPAC across the different phases of the motor task, which indicate that the variation in irPAC across movement stages is conserved in aging. We also found that coupling during the phase of low force production was weaker than both RAMP and higher force production phases in both old and young adults. This underlines the possibility that dynamic force contraction and higher forces require more inter-regional coupling in the beta-high gamma band from $cM1_{\varphi} \rightarrow iM1_{A}$. Thus, beta-high gamma irPAC may have relevance to motor output, where beta phase in cM1 is more tightly coupled to high gamma amplitude in iM1 to lock the iM1 to a baseline resting state. This could in part explain why higher coupling was observed during the 30% MVC phase, as well as why older adults showed stronger coupling than younger adults.

In contrast, higher **beta-low gamma coupling** was found in younger adults. In both groups, coupling was stronger in the 30%MVC phase compared to REST, ONSET and 15%MVC phases. Consistent with our findings in the beta-high gamma irPAC, 30%MVC requires more coupling in the $cM1_{\varphi} \rightarrow iM1_{A}$ direction. This stronger coupling may reflect an increasing demand to suppress iM1 during higher unimanual force production. However, it is important to note that irPAC in the beta-low gamma irPAC may not have the same role as beta-high gamma irPAC, as discussed earlier (Giustiniani et al., 2019; Omlor et al., 2007; Tzvi et al., 2016). The proposed transitional role of beta-low gamma suggests that during greater force production, more information processing is required than in the other phases, where high demand for the transformation of sensory information might be required to produce motor output.

In both gamma bands, we found that PAC followed a pattern during which **higher force production was associated with** significantly **more coupling** in the direction $cM1_{\varphi} \rightarrow iM1_{A}$. The PAC patterns across phases of the motor task did not resemble beta patterns in cM1, nor gamma patterns in iM1. Thus, strongest PAC was observed during the movement phase with the lowest beta power, while gamma power in iM1 did not change (since gamma power in iM1 should not be influenced by movement due to the lateralization of gamma activity to cM1 (D. Cheyne et al., 2008)). This suggests that gamma power in iM1 may be phase-locked to beta phase in cM1, effectively maintaining the iM1 in a resting state. This is in line with what has already been reported in previous studies who looked at beta-gamma PAC in the

context of PD and where an exaggerated coupling in the cortical-subcortical motor network was found to be associated with impaired motor performance scores (De Hemptinne et al., 2013; van Wijk et al., 2016).

When the driver cortex is iM1: $iM1_{\varphi} \rightarrow cM1_{A}$

In the $iM1_{\varphi} \rightarrow cM1_{A}$ direction where beta phase in iM1 is coupled to gamma amplitude in cM1, we found that younger adults had stronger beta coupling with both high and low gamma bands. This was especially the case in beta-low gamma irPAC, whereas in beta-high gamma irPAC, the difference between age groups was smaller. Since there was a lack of association between tPAC and motor performance, it remains unclear if this coupling is meaningful for the fine tuning of movement performance of the hand. There is currently no literature on beta-gamma coupling between cM1 and iM1. Thus, we are basing the interpretation of these results from previous work on the beta and gamma bands, as well as on concepts derived from neuronal communication theories.

In **beta-high gamma irPAC**, we observed stronger coupling during ONSET when compared to the 30% MVC phase (Fig. 12A). This means that coupling of these bands during the production of the higher force was the weakest, which is contrary to the results obtained in the opposite direction. This suggests that reduced coupling from $iM1_{\varphi} \rightarrow cM1_{A}$ may be necessary to produce higher level of force and that the reduced influence of the beta phase from iM1 on gamma amplitude in cM1 could be beneficial to movement production. This is coherent with our findings in the $cM1_{\varphi} \rightarrow iM1_{A}$ direction, where increased beta-high gamma irPAC might play a role in locking iM1 in a resting state, and where a reduced coupling might facilitate movement production in cM1. Although this can explain the role of PAC across the motor task phases, it does not explain how younger adults showed stronger coupling in $iM1_{\varphi} \rightarrow cM1_{A}$ irPAC. Since the magnitude of the difference in irPAC between the two age groups was small, it can be considered negligible.

A potential caveat in our results is that weaker coupling present during 30%MVC may simply be due to the decrease in beta power during that phase of the motor task (Xifra-Porxas et al., 2019). However, this is not the most probable explanation for the following reasons: this effect is not seen in the other direction $cM1_{\varphi} \rightarrow iM1_{A}$, and younger adults, who show a lower

absolute beta power, still have stronger irPAC in this direction. Hence, this particular effect may not simply be an artifact of beta power modulation and is more likely a valid form of PAC (Jensen et al., 2016).

In the **beta-low gamma irPAC**, whereas no differences across the phases of the motor task were observed, there was a significantly stronger coupling in young adults compared to older adults. As discussed previously, low gamma may not directly reflect movement production but rather a transitional role from sensory to motor information (Giustiniani et al., 2019; Omlor et al., 2007; Tzvi et al., 2016), where younger adults have higher efficiency.

Comparing directionality

In the **beta-low gamma PAC**, coupling strength was similar in the two directions. Overall, younger adults had greater irPAC values, with the effect being smaller when the driver was in cM1. As discussed previously, the lack of difference in terms of directionality suggests that the beta-low gamma irPAC is not necessarily representative of the lateralization from the task. Further studies are needed to better understand this type of coupling using non-dominant hand tasks or bimanual tasks.

For **beta-high gamma PAC**, beta phase in iM1 was coupled to gamma amplitude more strongly than in the opposite direction. In the $iM1_{\varphi} \rightarrow cM1_{A}$ direction when beta phase in iM1 was the driver for gamma amplitude in cM1, coupling during 30% MVC was the weakest, while for $cM1_{\varphi} \rightarrow iM1_{A}$,the same coupling during 30% MVC was the strongest. These results suggest that beta-high gamma irPAC between the motor cortices plays a phase-locking role where beta phase prevents the high gamma band from performing a pro-kinetic role. Furthermore, when the driver was cM1, irPAC was weaker and older adults showed stronger coupling in this direction. The difference observed in the directionality of irPAC is likely influenced by the lateralized nature of the task. This result supports the idea that beta-gamma uncoupling facilitates movement production while coupling phase-locks gamma promotes a resting state.

While this is coherent with studies that looked at beta-gamma PAC in PD patients and where it was shown that stronger beta-gamma coupling was associated with more impaired motor performance, this is contrary to studies performed in older subjects where stronger theta-

gamma PAC was shown to be beneficial to memory and cognitive performance (Reinhart & Nguyen, 2019). The role of PAC may be due to the type of information transmitted in the low frequency (Assenza et al., 2017) and the type of reciprocal connection (excitatory vs inhibitory) (Nandi et al., 2019). Future research on this topic is needed for a better understanding of PAC in the motor domain.

ASSOCIATIONS BETWEEN PAC & MOTOR PERFORMANCE

We found one very weak correlation between local PAC and performance on the tasks. As discussed previously, one reason why our results remain inconclusive is that our motor task was not engineered to induce error: our error values were small and mostly clustered around 0 (no error). The lack of association can also be attributed to fact that generalization of the main modes of coupling was obtained from a subset of patients and that we did not find convincing main modes of coupling from the local PAC analyses. This might explain why we did not find consistent trend of local PAC with the phases of the motor tasks, as the main modes of coupling were not individualized to an optimal range.

LIMITATIONS

This is the first study that looked at beta-gamma band interaction during hand movement in bilateral M1s in the context of aging. There are several limitations to this study.

It has been shown that PAC was more engaged during learning and accrued attention states (Szczepanski et al., 2014). Since the tasks used as part of this experiment were easy, it is possible that they did not require strong modulation of PAC, hence explaining weak changes in PAC across the phases of the motor task. Consequently, the neurophysiological modulation of local and irPAC due to age was based on the assumption that older adults generally show impaired motor performance in comparison to their younger counterpart, as observed on our standardised clinical tests. 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 PAC.

The irPAC analysis lacked surrogate data to compare to, which did not allow us to extract statistical scores. This step is important in order to control for false positives (Gohel et al., 2016) and is an important limitation that needs to be addressed in future studies.

The main modes of coupling for single band tPAC were generalized from a subset of our participants. We chose to not run full PAC on each subject due to time constraints. Identifying the main mode of coupling for each subject might be a better strategy in order to individualize optimal coupling within the beta and gamma bands. Hence, future studies should consider identifying modes of coupling for each subject instead of generalizing the main modes of coupling from a subset of participants.

We found a significant main effect due to motor task phase in local beta-low gamma PAC in cM1 for unimanual task, however, the post-hoc results were non-significant. Although this might be because main modes of coupling were not identified for local PAC, another possibility is that the smaller number of participants led to insufficient power on the statistical tests.

We also found that the identified M1 area might not be exactly on the hand knob (Appendix I, Fig.7). Due to the nature of PAC analysis, finding its exact location is necessary to avoid mixing signals from other parts of M1 such as leg or face areas.

Last, we did not explore other modes of coupling such as theta, delta or alpha as frequencies for phase as part of our analysis. For example, theta-gamma and alpha-gamma coupling were both shown to play a role in learning paradigms (Nowak et al., 2017; Tzvi et al., 2016, 2018; Yanagisawa et al., 2012), which indicates that they are valid frequencies to explore in future analyses.

CHAPTER V | CONCLUSION

SIGNIFICANCE

Currently, there is compiling evidence for beta and gamma band activity to play roles in the planning, initiation and execution phases of motor performance but to date, there is limited evidence about the role played by the coupling of both frequencies. This study is the first one to look at beta-gamma PAC in the context of aging in the motor domain. This includes the quantification of reciprocal connections in the beta-gamma bands between M1s during the performance of motor tasks.

Our findings reveal an age-related change in PAC within cM1 and iM1. In general, our results support the hypothesis that beta-gamma PAC in bilateral M1s has a "phase-locking" effect that hinders the pro-kinetic gamma oscillation necessary for movement production.

In conclusion, the work presented in this manuscript contributes to a better understanding of oscillatory brain patterns present during handgrips tasks in the healthy aging population via neuronal cross-frequency coupling.

This knowledge can contribute to the development of individualized interventions based on non-invasive brain stimulation techniques such as tACS in the presence of aberrant brain oscillations such as in PD or autism population as well.

CHAPTER VI | REFERENCES

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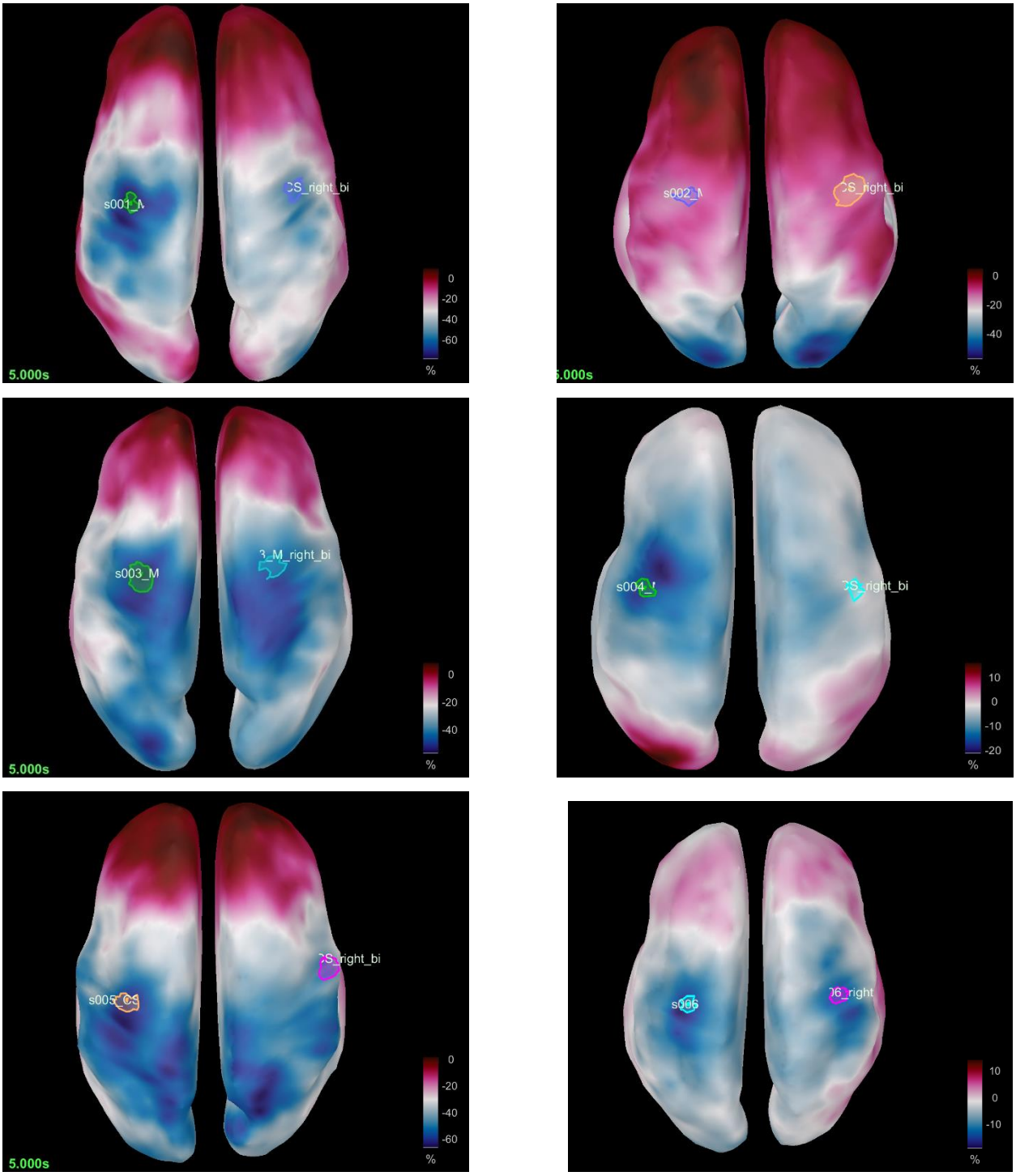
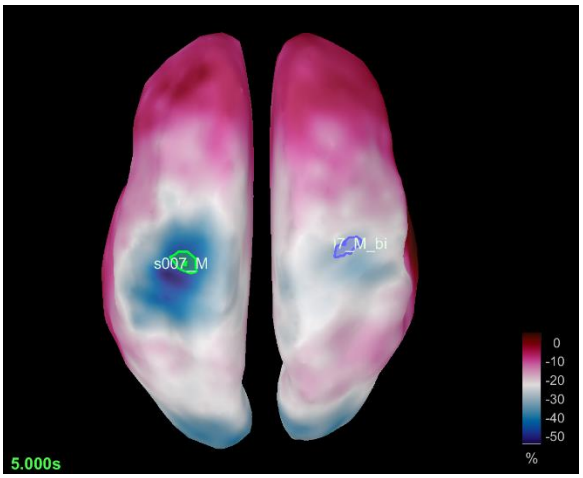
CHAPTER VII | APPENDICES

APPENDIX I: M1 HAND REGION LOCALIZATION FROM TIME-FREQUENCY MAPS

Regions identified as M1 bilaterally for each participant.

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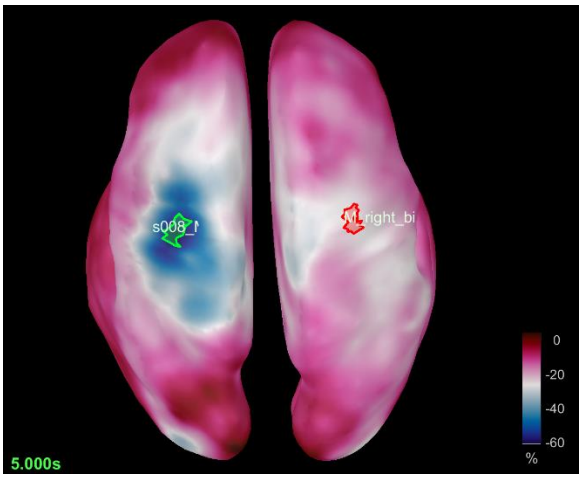
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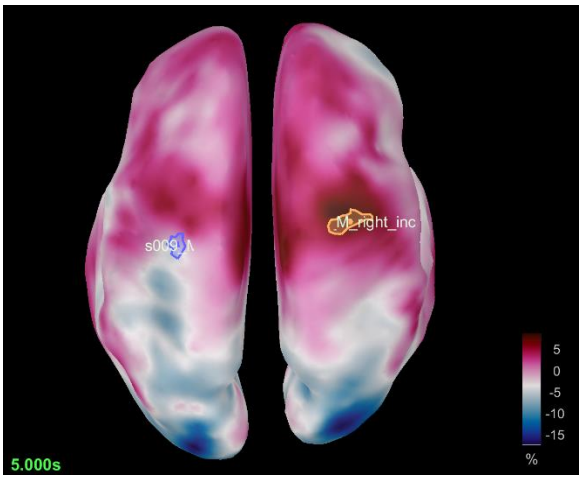
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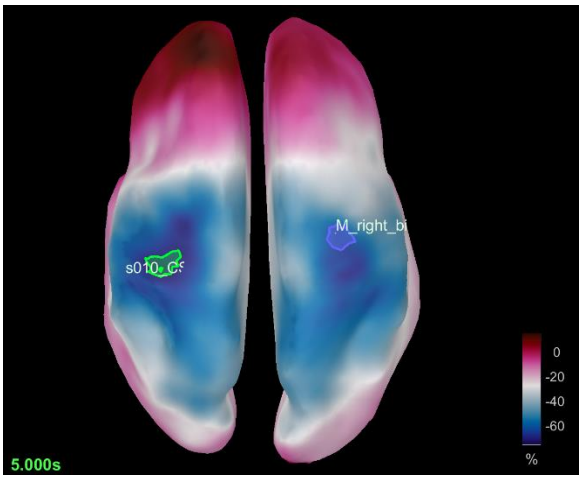
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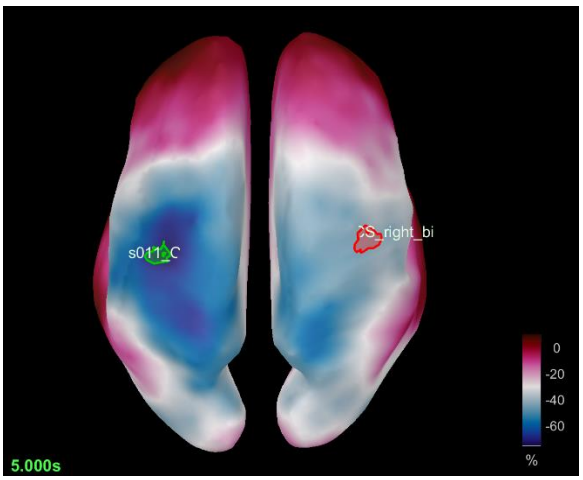
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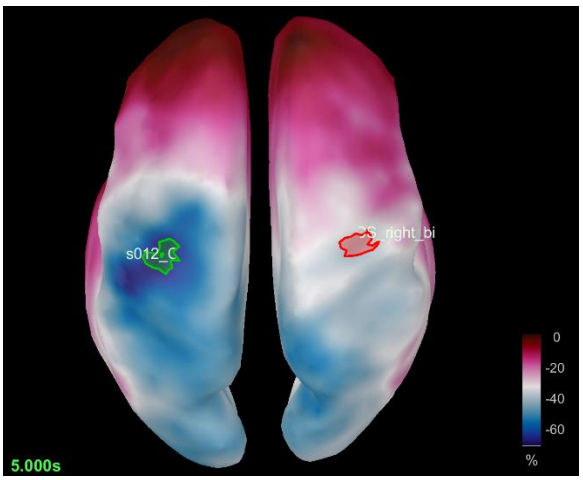
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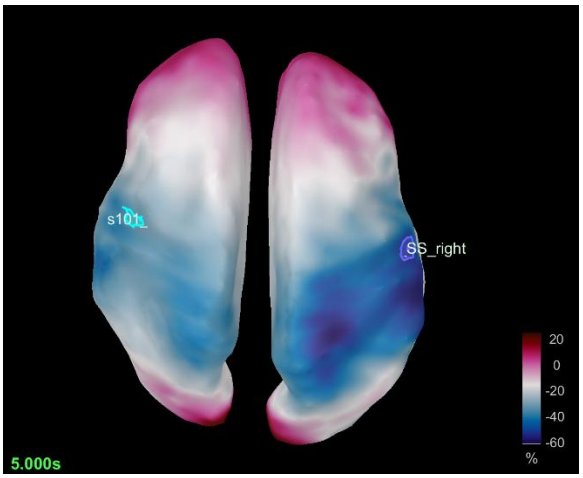
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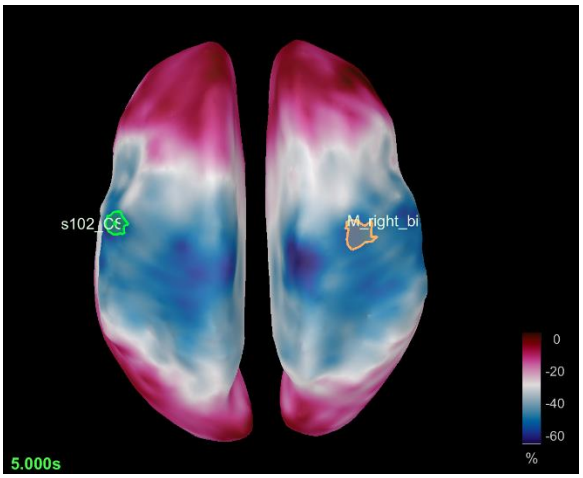
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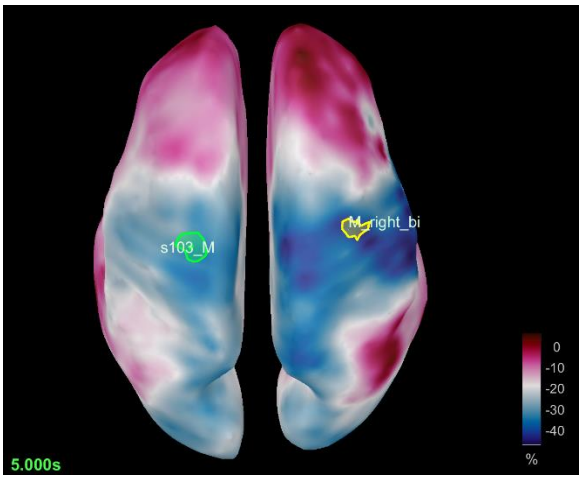
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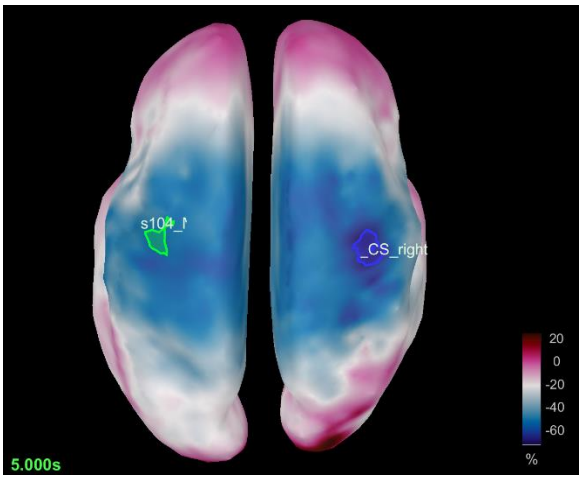
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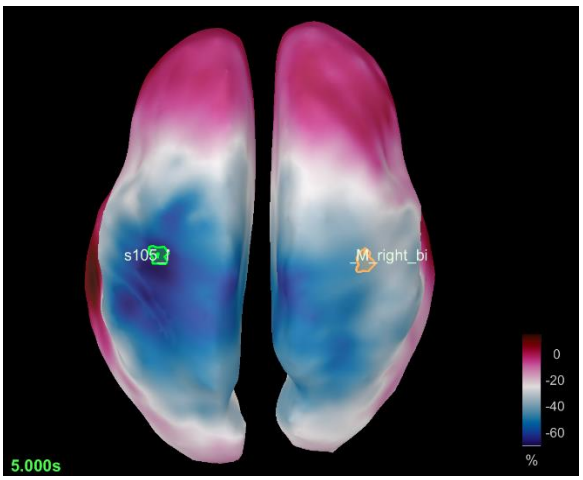
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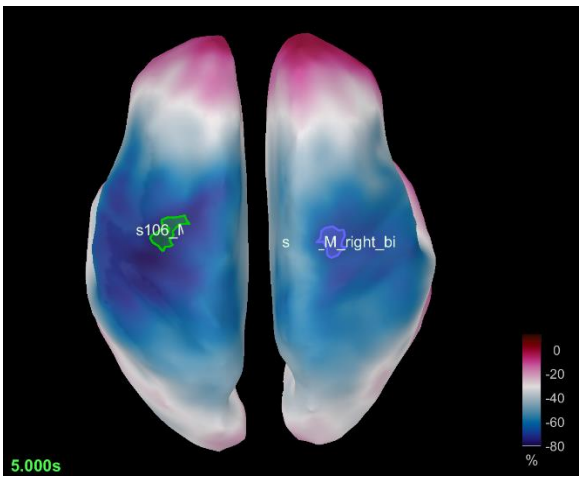
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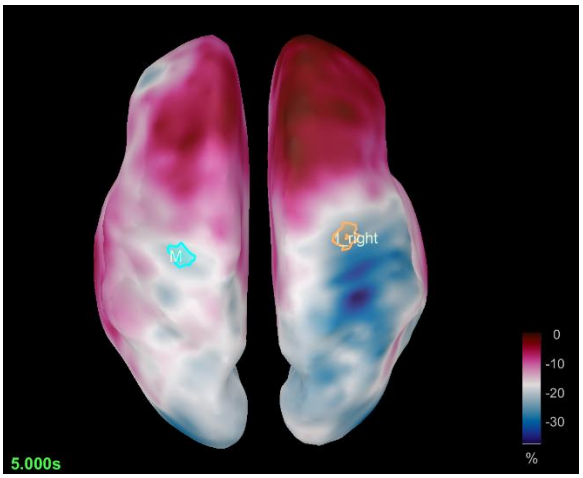
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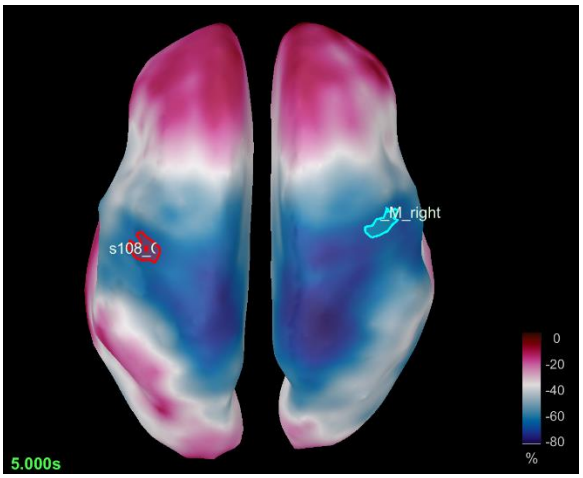
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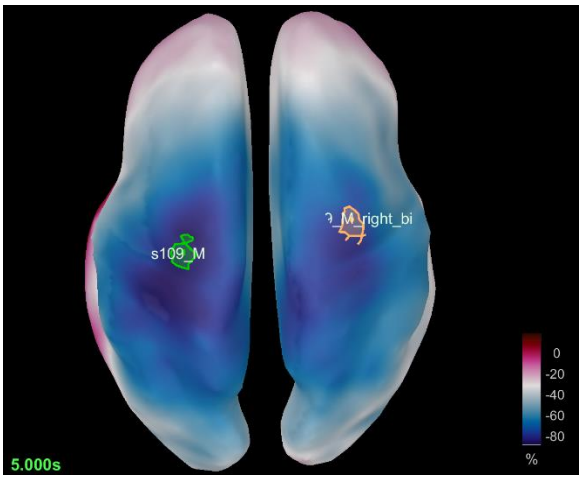
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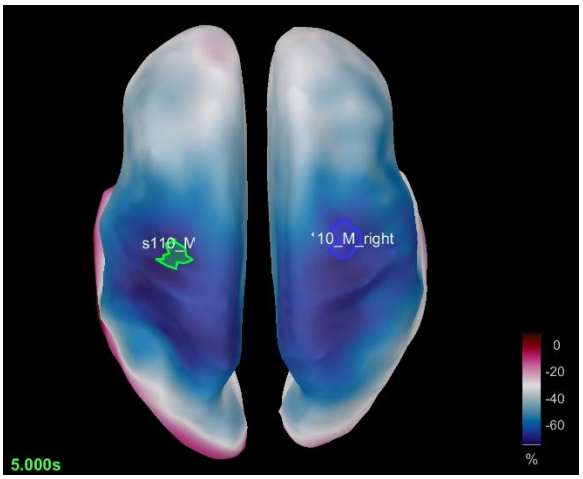
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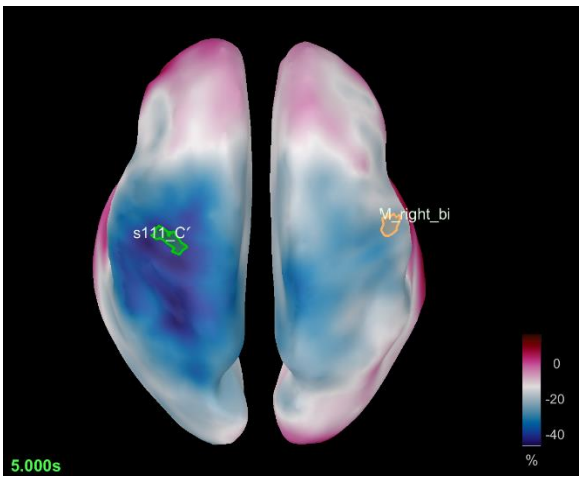
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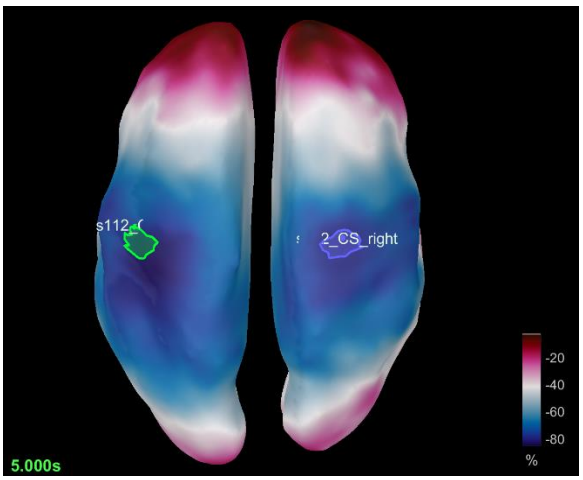
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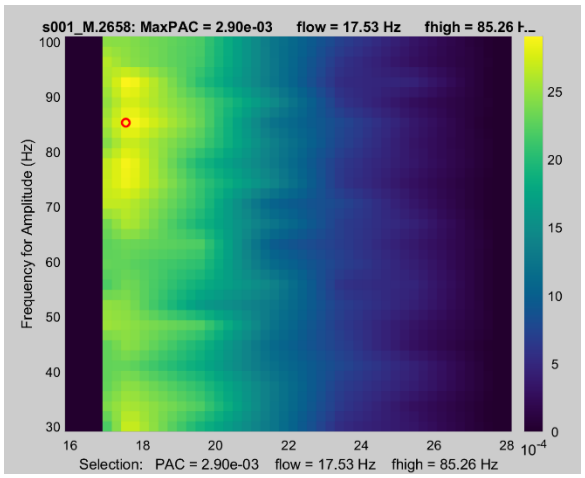
APPENDIX II: RESULTS FROM MAIN MODE OF COUPLING ANALYSIS

In this section, the results from the multiple band / full tPAC analyses are presented. From these graphs, the main modes of coupling were extracted. 6 out of 24 participants were selected randomly to run these analyses (3 old).

For each of the following images, the y-axis represents the tested frequencies for amplitude in the gamma band (30-100Hz), and the x-axis represents the frequencies for phase (16-28 Hz). A brighter color represents stronger coupling.

Section i: Local PAC

A



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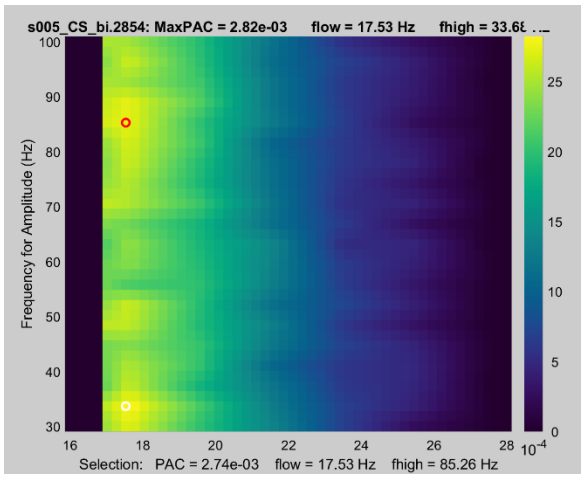

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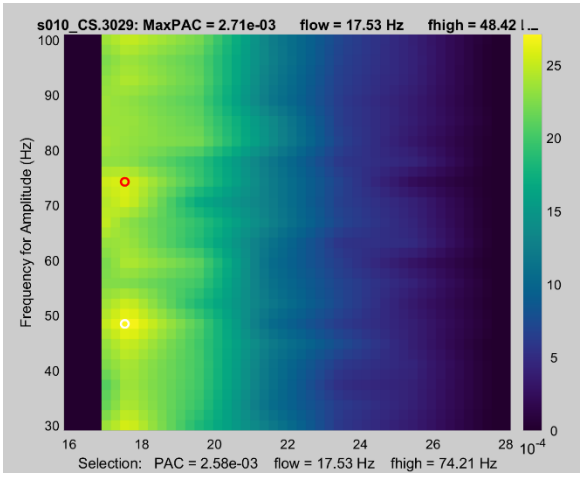

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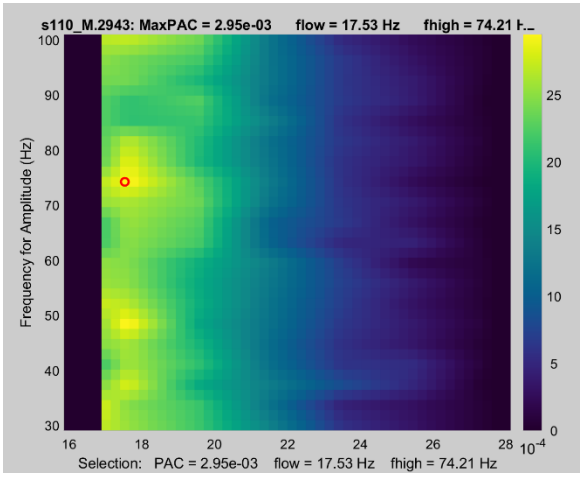
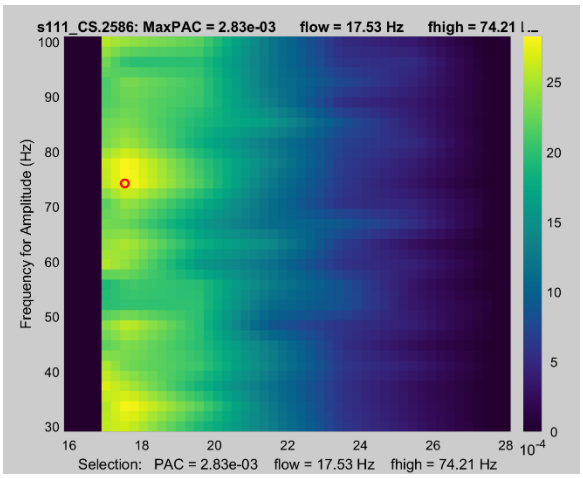
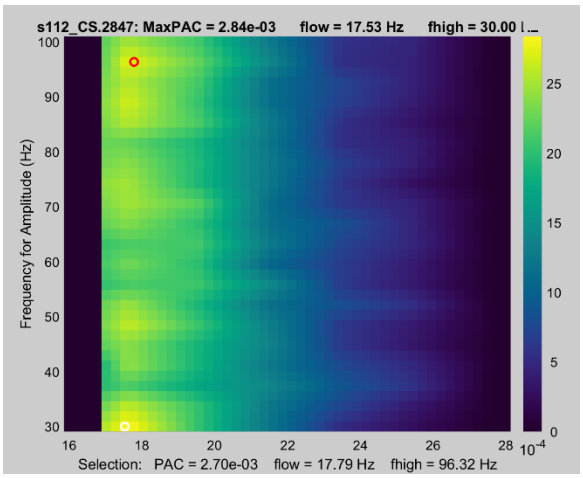
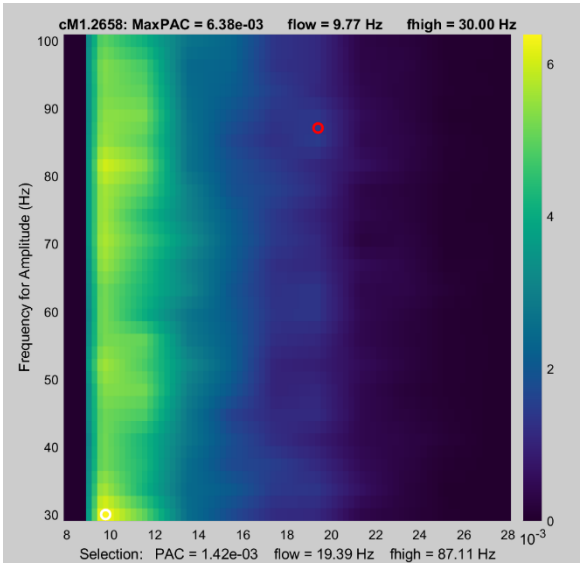


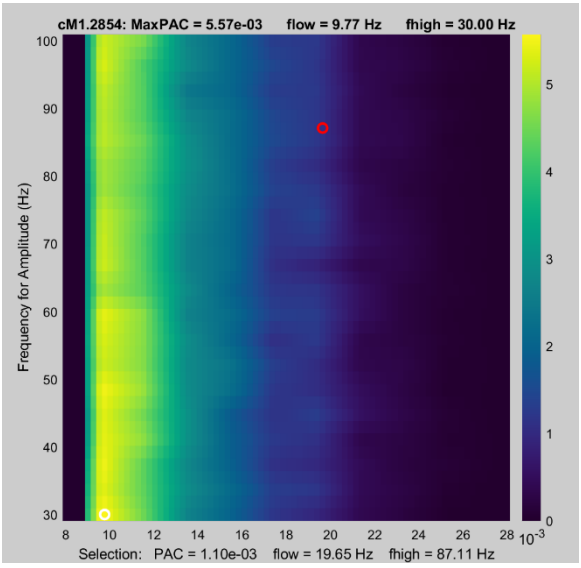
E 

F 

These comodulograms show that stronger coupling was present only in the lower beta frequencies while smoothly tending towards 0 at higher beta frequencies. Since phase is more easily extracted at lower frequencies, this suggests that the coupling found here is a computational artifact and that the stronger coupling at the lower beta ranges is only due to a more easily extracted phase.

To confirm this upon review, we extended the frequency range for phase into the alpha range to have a complete range from 8-28 Hz. Our results show that the smooth decrease is still present (compare to the inter-regional comodulograms results).

G 

H 

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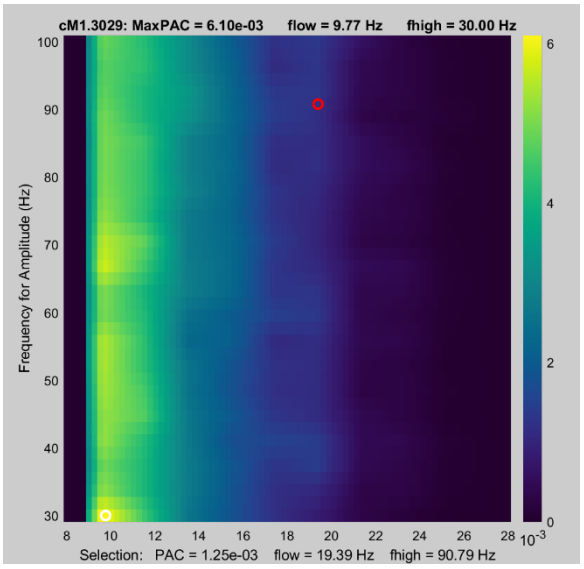
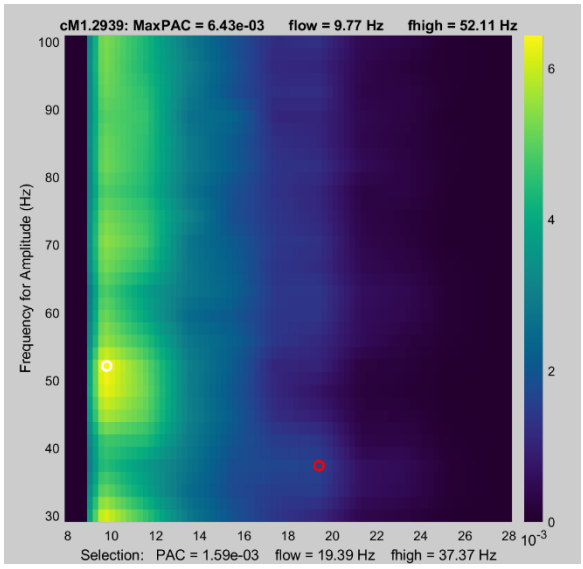

cM1.3029: MaxPAC = 6.10e-03 flow = 9.77 Hz fhigh = 30.00 Hz
Frequency for Amplitude (Hz)
Selection: PAC = 1.25e-03 flow = 19.39 Hz fhigh = 90.79 Hz
10^-3

J


cM1.2939: MaxPAC = 6.43e-03 flow = 9.77 Hz fhigh = 52.11 Hz
Frequency for Amplitude (Hz)
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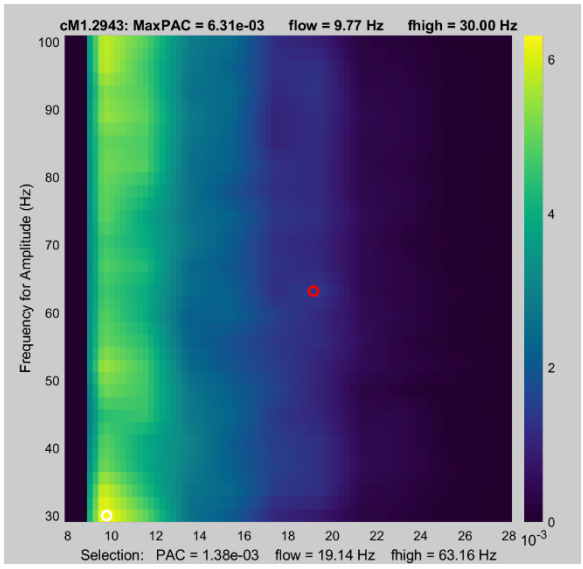
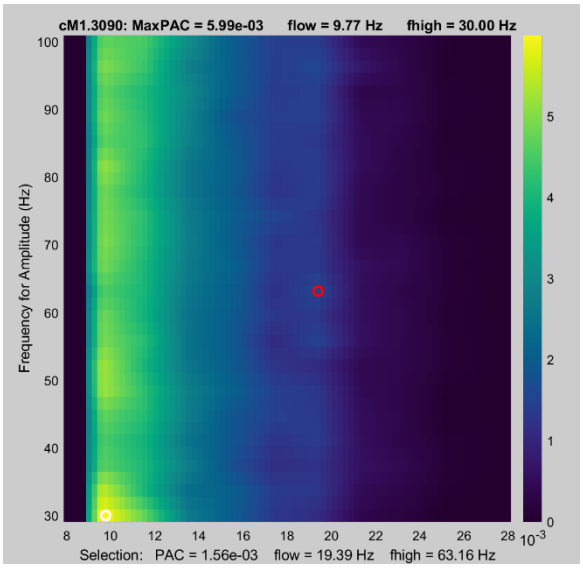
10^-3

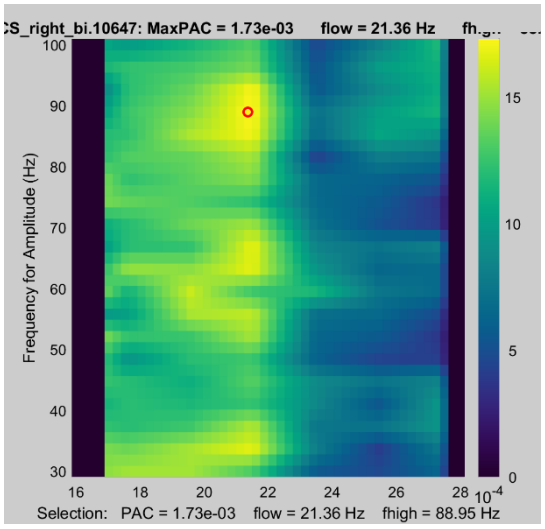
K


cM1.2943: MaxPAC = 6.31e-03 flow = 9.77 Hz fhigh = 30.00 Hz
Frequency for Amplitude (Hz)
Selection: PAC = 1.38e-03 flow = 19.14 Hz fhigh = 63.16 Hz
10^-3

L


cM1.3090: MaxPAC = 5.99e-03 flow = 9.77 Hz fhigh = 30.00 Hz
Frequency for Amplitude (Hz)
Selection: PAC = 1.56e-03 flow = 19.39 Hz fhigh = 63.16 Hz
10^-3

Section ii: Inter-regional PAC, seed in cM1



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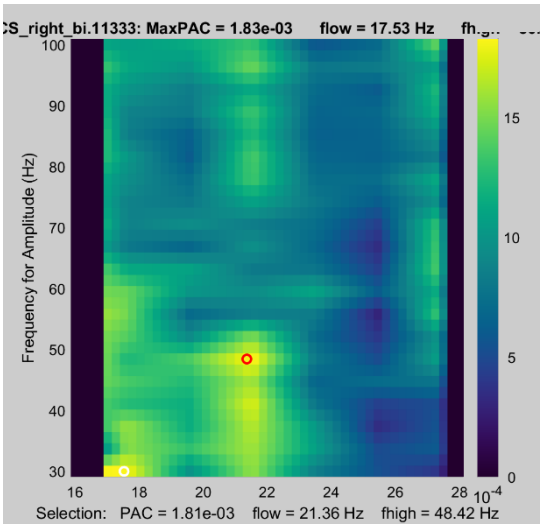

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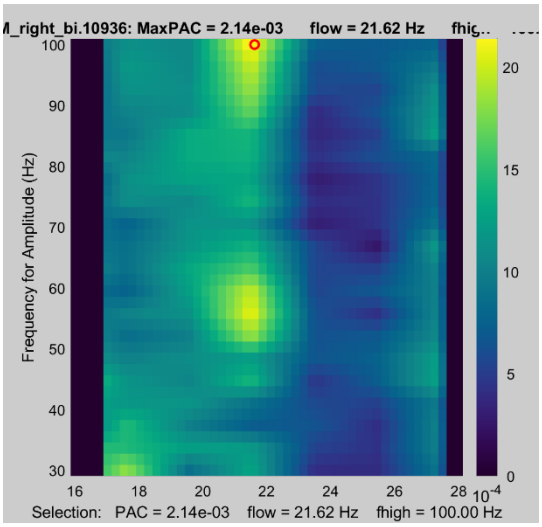

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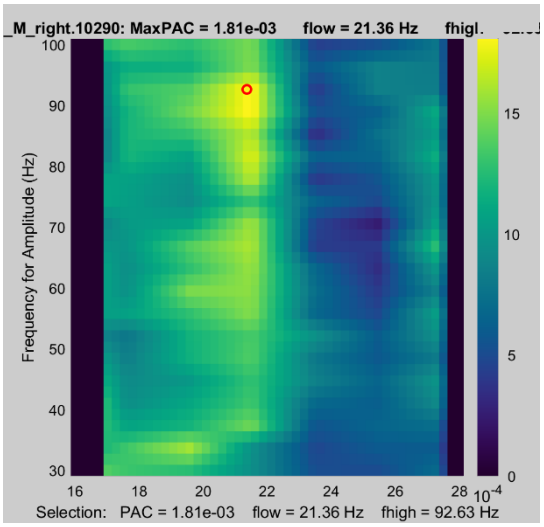

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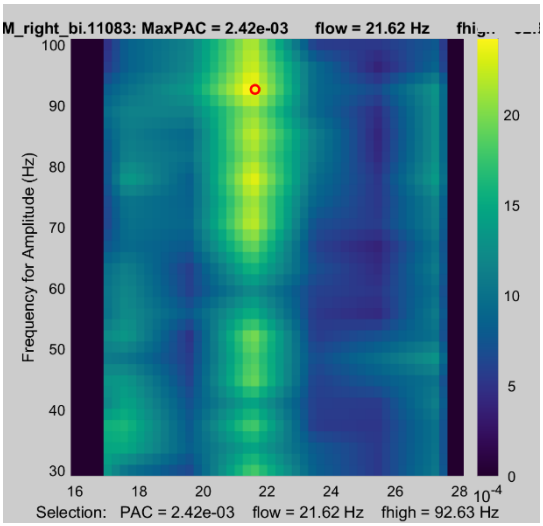

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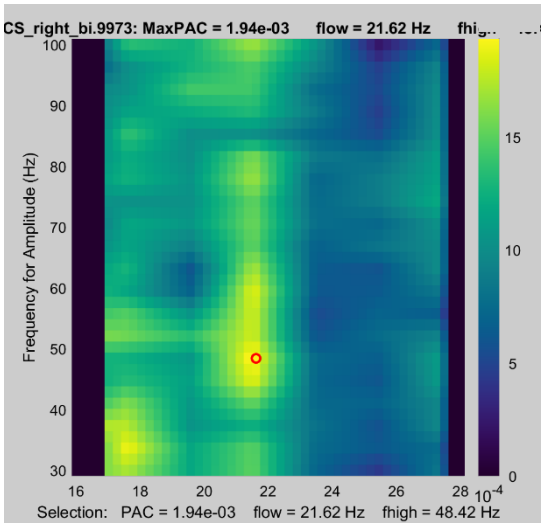

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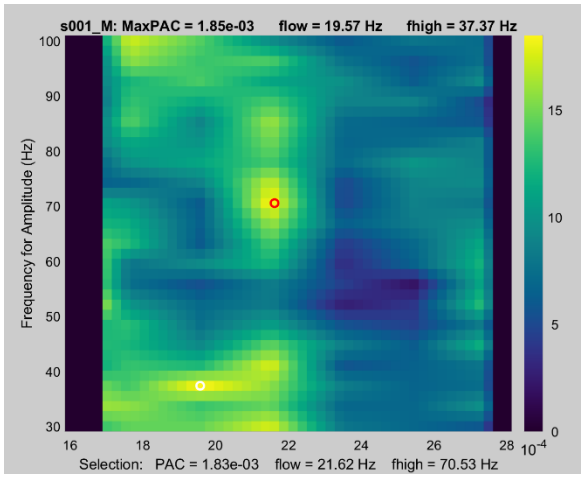
Section iii: Inter-regional PAC, seed in iM1



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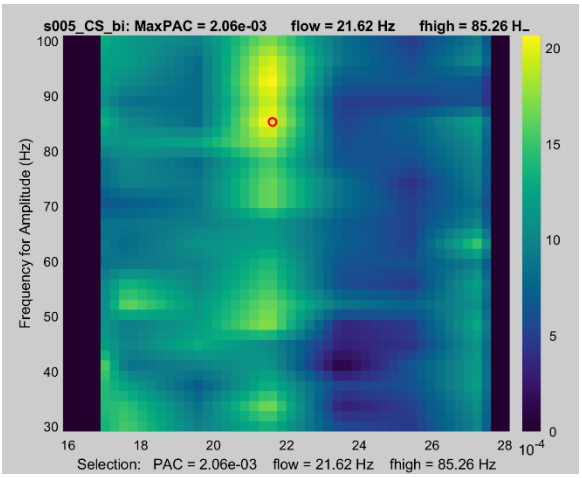

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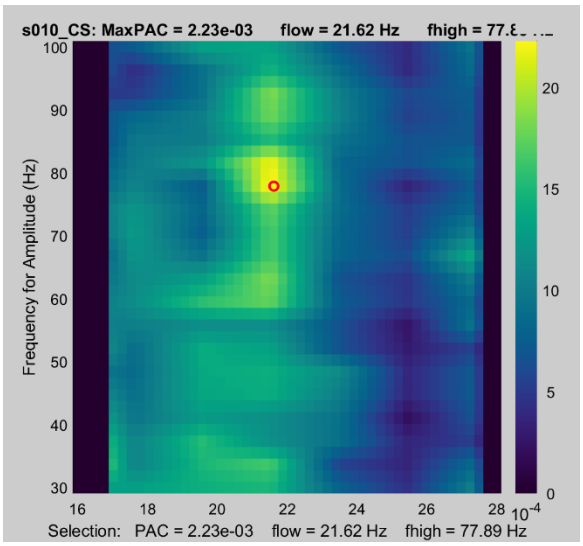

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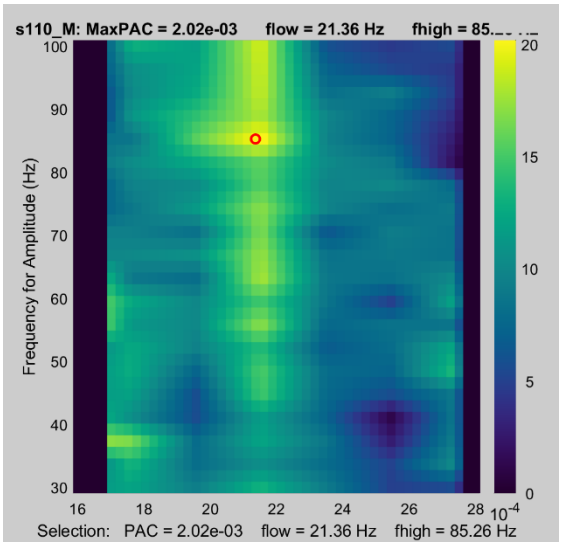

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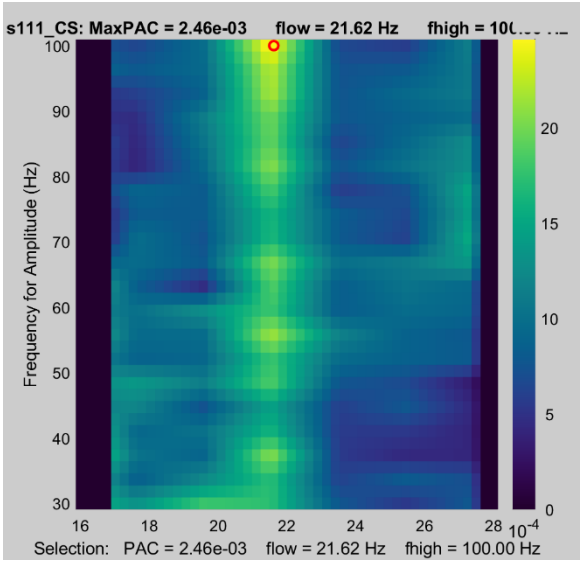

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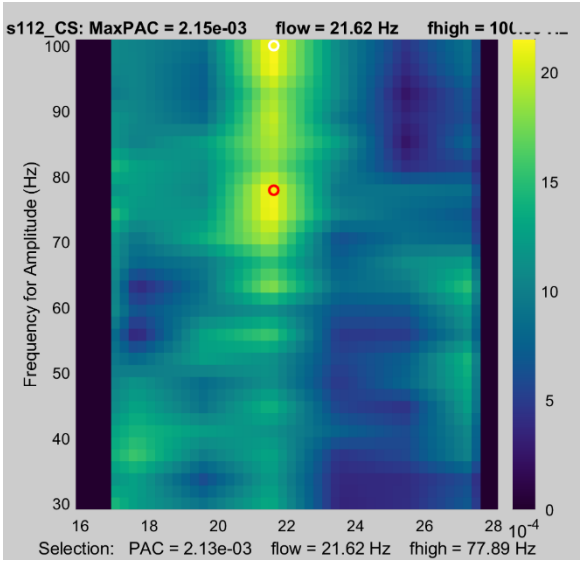

F

APPENDIX III: JUPYTER NOTEBOOKS FOR STATISTICS & GRAPHS

The notebooks are presented in the following order:

1. Motor performance results
2. Unimanual local tPAC results
3. Bimanual local tPAC results
4. Unimanual irPAC results
5. Unimanual local tPAC correlation results
6. Bimanual local tPAC correlation results