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The neurophysiological changes associated with motor learning in adults and adolescents

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THE NEUROPHYSIOLOGICAL CHANGES ASSOCIATED WITH MOTOR LEARNING IN ADULTS AND ADOLESCENTS

by

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THE NEUROPHYSIOLOGICAL CHANGES ASSOCIATED WITH MOTOR LEARNING IN ADULTS AND ADOLESCENTS

James E. Gehringer, Ph.D.

University of Nebraska, 2019

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One main purpose of this dissertation was to explore how sensorimotor cortical oscillations changed after practicing a novel ankle plantarflexion target matching task. We behaviorally quantified the speed, accuracy, reaction time, velocity, and variability of the participant's performance of the task, while collecting their neurophysiological responses with magnetoencephalography (MEG). With these data, we assessed how the motor planning and execution stages of movement during a goal directed target matching task changed after practicing a task in typically developing young adults with their non-dominant ankle. We found that the cortical oscillations in the beta frequency range that were sourced from the sensorimotor and occipital cortices were weaker after practice. These individuals also improved behaviorally, with faster speed, greater accuracy, higher velocity, and less variability. The decreased strength likely reflects a more refined motor plan, a reduction in neural resources needed to perform the task, and/or an enhancement of the processes that are involved in the visuomotor transformations that occur prior to the onset of the motor action.

The second purpose was to explore how the changes of the sensorimotor cortical oscillations after practicing a novel ankle plantarflexion target matching task differ between adults and adolescents. We assessed these behavioral and neurophysiological changes in a cohort of typically developed adults and adolescents. After practice, all of the participants matched more targets, matched the targets faster, had improved accuracy, faster reaction times, and faster force production. However, the motor performance of the

adults exceeded what was seen in the adolescents regardless of practice. In conjunction with the behavioral results, the strength of the beta ERD across the motor planning and execution stages was reduced after practice in the sensorimotor cortices of the adolescents, but was stronger in the adults. These outcomes suggest that there are age-dependent changes in the sensorimotor cortical oscillations after practice, which might be related to familiarity with the motor task.

The third purpose was to explore how movement attenuates the somatosensory cortical oscillations and how this attenuation differs in adults and adolescents. We used MEG to address this knowledge gap by applying an electrical stimulation to the tibial nerve as adolescents and adults produced an isometric ankle plantarflexion force, or sat quietly with no motor activity. We found movement-related attenuation of the somatosensory oscillations. Attenuation of the alpha-beta ERS while producing the isometric force was greater in adolescents when compared with adults, while the adults had a greater attenuation of the beta ERD. These results imply that alterations of frequency specific somatosensory cortical oscillations may partly underlie the altered motor performance characteristics seen in adolescents.

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LIST OF ABVREVIATIONS

BESA	Brain Electrical Source Analysis
CNS	Central Nervous System
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
ECoG	Electrocorticography
EEG	Electroenchephalography
ERD	Event Related Desynchronization
ERP	Event Related Potential
ERS	Event Related Synchronization
FA	Fractional Anisotropy
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GABA	γ-aminobutyric acid
M1	Motor Cortex
MD	Mean diffusivity
MEG	Magnetoenchephalography
MPRAGE	Magnetization-Prepared Rapid Acquisition with Gradient Echo
MRI	Magnetic Resonance Imaging
PET	Proton Emission Tomography
PMBR	Post Movement Beta Rebound
preSMA	Presupplementary Motor Area
S1	Primary Somatosensory Cortex
SMA	Supplementary Motor Area
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences

INTRODUCTION

Motor Control

The internal model is the representation in the brain of how a movement will be performed and what the expected outcome will be (Figure 1; Huang et al., 2011; Hwang & Shadmehr, 2005; Kluzik et al., 2008; Milner & Franklin, 2005; Smith & Shadmehr, 2005; Thoroughman & Shadmehr, 1999). These representations are the most optimized motor plan based on prior experience and are assumed to recruit only the ideal muscle synergies to accurately control the motor action (Huang et al., 2011; Hwang & Shadmehr, 2005; Kluzik et al., 2008; Milner & Franklin, 2005; Smith & Shadmehr, 2005; Thoroughman & Shadmehr, 1999). Before a motor action occurs, an internal model is used to make feed-forward predictions on what muscle synergies are needed to perform the motor action efficiently and accurately (Shadmehr, 2004; Wolpert, 2007). Once the motor action is executed, online corrections are made to guide the action towards success through the

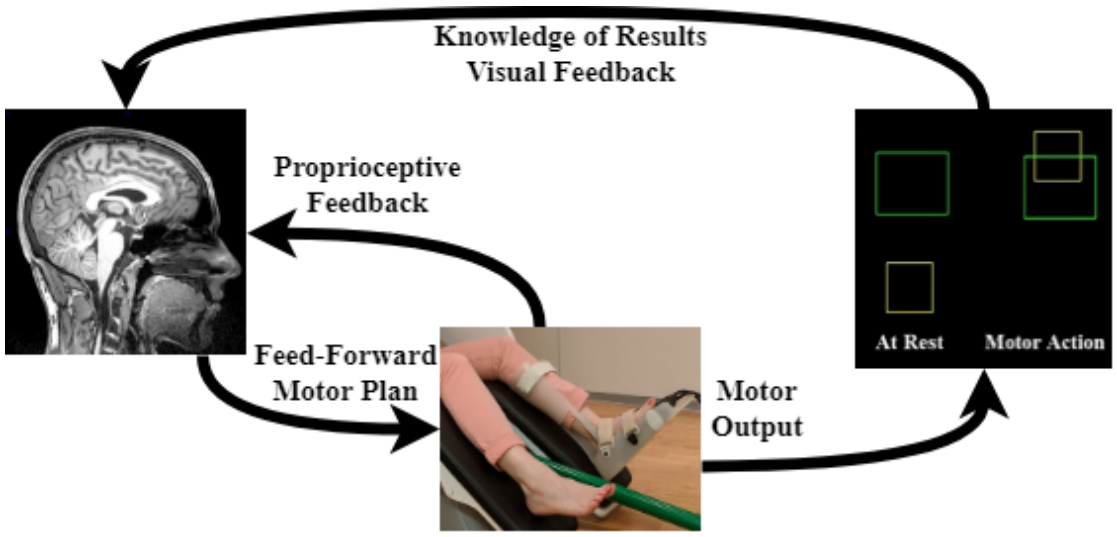

Figure 1: Model for Completing Goal Directed Movements. Conceptual scientific framework of the sensorimotor transformation, execution, and sensory feedback stages that are involved in completing a goal directed motor task. These stages are based on an internal model that is used to predict the ideal muscle synergies required to achieve the desired goal. Sensory information is used during the formulation of the motor plan, during the online corrections during the movement, and after the movement, along with the knowledge of results, to optimize the internal model.

use of sensory feedback networks (*e.g.* proprioceptive and visual sensory feedback). In the event the motor action was successful in achieving the desired goal, the internal model is then updated using the current sensory information to build a more representative model of an accurate motor action (Doyon & Benali, 2005; Willingham, 1998). In the event the motor action was not successful, the current sensory state is stored in relation to how the motor action termination was incorrect, in order to make more informed corrections for future movements (Doyon & Benali, 2005; Willingham, 1998). While the internal model and its iterative optimization process is well appreciated, there is little understanding of how the sensorimotor oscillatory activity that drives motor control changes as the internal model is updated after practice.

Oscillatory Activity of Motor Control

There is a well-established pattern of activity that occurs in the beta band (about 15 – 30 Hz; Figure 2) any time a volitional movement is executed. This pattern of activity has two major parts, the beta event related desynchronization (ERD) and the post-movement beta rebound (PMBR). The beta ERD begins to occur slightly before a motor action is executed. This pre-movement beta ERD is thought to be the formulation of the motor plan, the internal model being referenced to make the necessary feed-forward predictions for a successful performance given the task constraints. Following the

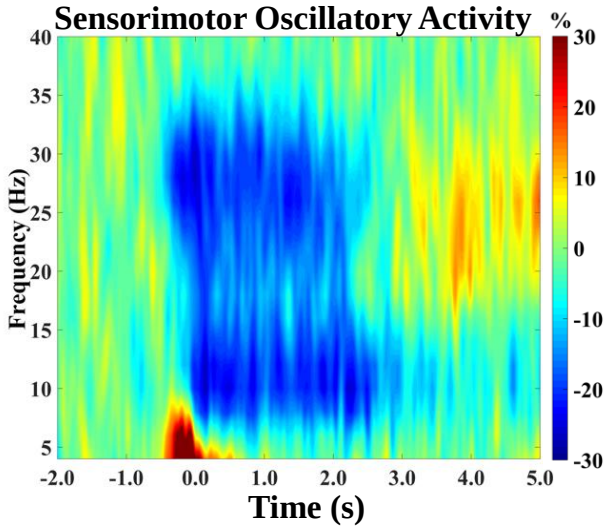

Figure 2: Exemplary group-averaged time-frequency spectrogram of the motor oscillatory activity. Exemplary time-frequency plot for a MEG sensor that over the motor region of the cortex. Beta ERD (blue, 15 – 30 Hz) occurs before movement onset and represents the cortical activity during the motor planning stage. The alpha ERD (blue, 8 – 14 Hz) occurs at movement onset.

execution of the motor action, the beta ERD is sustained until the movement is terminated. This peri-movement beta ERD is considered the online monitoring of the movement through use of the proprioceptive and visual sensory systems in order to make adjustments to achieve the desired goal. Typical beta ERD responses involve widespread bilateral activity across the sensorimotor cortical areas, with the strongest maxima contralateral to the effector producing the motor action and following the basic homuncular topology of the pre/post central gyri. Additional areas of concurrent beta ERD activity often include the premotor area, SMA, parietal cortices, and mid cingulate.

The post-movement beta rebound then occurs after the termination of the movement. There are a variety of theories about the function of the PMBR. The PMBR is thought to be largely an inhibitory response, deactivating the motor cortex (Gaetz et al., 2010a). Other studies suggest the PMBR is related to the updating of the internal model or the return of sensory feedback (Fry et al., 2016; Gaetz & Cheyne, 2006; Houdayer et al., 2006; Parkes et al., 2006; Pfurtscheller et al., 2001a; Pfurtscheller et al., 2005; Pfurtscheller et al., 2001b; Reyns et al., 2008; Tan et al., 2014a; Tan et al., 2016; Tan et al., 2014b). These activations are generally strongest in the contralateral primary sensorimotor cortices (M1/S1), supplementary motor area (SMA), the parietal lobe, and cerebellum.

Additionally, there are activations in the alpha band (8 – 14 Hz) that occur during the execution of a motor action (Leocani et al., 1997; Pollok et al., 2014; Zhuang et al., 1997). The alpha ERD begins at motor execution and persists until the motor action is terminated. This alpha desynchronization is thought to represent the attentional demands for the task (Pollok et al., 2014; Zhuang et al., 1997). Although there is plenty of investigations into motor control and its associated oscillatory activity, there is a scarcity of work looking at how this activity changes after practice.

Motor Learning

Motor learning occurs through the iterative optimization of the internal model. The internal model is updated after the termination of a motor task, using a combination of a knowledge of the result of the motor action and the visual and somatosensory feedback. Motor learning occurs over a number of trials and in three distinct stages (Dayan & Cohen, 2011; Doyon & Benali, 2005; Doyon & Ungerleider, 2002; Fischer et al., 2005; Korman et al., 2003; Muellbacher et al., 2002; Robertson et al., 2004; Walker et al., 2002). The first stage is fast motor learning. During this stage there are rapid improvements in the task performance after a single practice session. Furthermore, the largest behavioral gains are made in both magnitude and rate of learning during fast motor learning (Doyon & Benali, 2005; Karni et al., 1995; Ungerleider et al., 2002). Fast motor learning has been shown to change the activity in dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), presupplementary motor area (preSMA), premotor cortex, supplementary motor area (SMA), parietal regions, striatum, and the cerebellum (Dayan & Cohen, 2011; Floyer-Lea & Matthews, 2004, 2005; Grafton et al., 2002; Honda et al., 1998; Sakai et al., 1999). These changes in activity are thought to reflect not only the recruitment of additional neural substrates after practice but also the consolidation of the previously employed neural resources as the internal model becomes more efficient (Poldrack, 2000).

The second stage, the slow motor learning stage, is where incremental improvements are made across multiple practice sessions. During this stage, the behavioral gains tend to be slower than the gains in the fast motor learning stage and the rate of improvement decreases. During slow motor learning, changes in activity have been noted in the primary motor cortex, somatosensory cortex, SMA, putamen, and the cerebellum (Floyer-Lea & Matthews, 2004, 2005; Lehericy et al., 2005). These changes during slow motor learning are in more posterior regions of the brain compared to fast

motor learning (Dayan & Cohen, 2011). This locational shift is thought to reflect the change in attentional and executive functions, as the task becomes more automatic with practice (Kelly & Garavan, 2005). Further investigations have also found structural changes associated with the slow motor learning stage, in both grey and white matter of the brain (Bengtsson et al., 2005; Bermudez & Zatorre, 2005; Boyke et al., 2008; Cannonieri et al., 2007; Draganski & May, 2008; Driemeyer et al., 2008; Gaser & Schlaug, 2003; Han et al., 2009; Jäncke et al., 2009; May & Gaser, 2006; Park et al., 2009; Sampaio-Baptista et al., 2013; Schmithorst & Wilke, 2002; Scholz et al., 2009; Taubert et al., 2010).

The third stage, the offline learning stage, is where the motor memories are consolidated and skill stabilization occurs. Consolidation is the behavioral improvements that occur between practice sessions and the increase in strength of the motor memory after encoding (Robertson, 2009; Robertson et al., 2004). Prior investigations have suggested that the motor memory consolidation occurs in the primary motor cortex, striatum, and hippocampus (Albouy et al., 2008; Debas et al., 2010; Doyon & Ungerleider, 2002; Fischer et al., 2005; Muellbacher et al., 2002; Robertson et al., 2005). These three stages together can lead to long-term retention of a motor action, even with small doses of training over short amounts of time (Savion-Lemieux & Penhune, 2005).

Somatosensory Oscillatory Activity

Given that the internal model is updated based on a combination of the knowledge of results and the sensory feedback, it would be more difficult to improve at a motor skill without accurate somatosensory feedback. It is well recognized that peripheral stimulation of the foot while sitting quietly produces an immediate and transient event-related synchronization (ERS) of the somatosensory cortical oscillations across the 10-75 Hz

frequency bands (Figure 3; Kurz et al., 2014b; 2015; 2017b; Wiesman et al., 2017). These neural synchronizations are followed by a desynchronization across the alpha (8-16 Hz) and beta (18-26 Hz) and frequency bands during the later time window (150 ms-400ms). The ERS is the strongest in the somatosensory cortex contralateral to the peripheral stimulus and follows the basic homuncular topology of the post central gyrus. Further, the somatosensory network has been shown to involve the parietal operculum, the posterior parietal cortex, the prefrontal cortex, and the thalamus (Mauguiere et al., 1997).

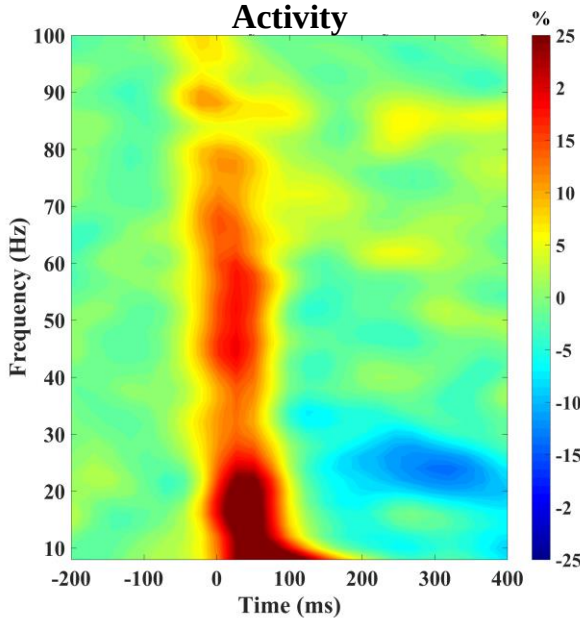

Figure 3: Exemplary group-averaged time-frequency spectrogram of the somatosensory response. Exemplary time-frequency plot for a MEG sensor that over the somatosensory region of the cortex. Broadband ERS (red, 8 – 80 Hz) occurs at stimulation onset. The beta ERD (blue, 18 – 26 Hz) occurs after the stimulation.

However, movement can modulate this somatosensory response. Predominantly, our understanding of movement-related somatosensory attenuation (i.e., gating) has been derived from event related potential (ERP) studies of peripheral nerve stimulation (Jones et al., 1989; Kristeva-Feige et al., 1996; Macerollo et al., 2016; Papakostopoulos et al., 1975). Overall these studies have shown that the amplitude of the evoked somatosensory cortical activity is attenuated during movement (Houdayer et al., 2006; Neuper et al., 2006). It has also been shown that the neural synchronizations seen across the theta-beta frequency range (6-24 Hz) are sustained while performing a haptic task, while the other frequency bands that were seen in the no movement condition are completely gated (Kurz

et al., 2018). Although the knowledgebase on how changes in the strength of the somatosensory cortical oscillations reflect the differences in sensory processing is growing, whether these cortical oscillations are different between adolescents and adults during movement remains unknown.

Motor Control in Adolescence

Although motor control and motor learning has been well explored in typically developed adults, there is little work exploring the cortical dynamics of motor control and motor learning in adolescents. Behaviorally, adolescents tend to have greater variability in their movements, but the variability diminishes with age. During single joint movements, drawing, aiming, reaching, and grasping tests, adolescents demonstrated greater mastery of the task with increased age (Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Fayt et al., 1992; Hay et al., 1991; Jansen-Osmann et al., 2002; Kuhtz-Buschbeck et al., 1998; Yan et al., 2000). There is no consensus why motor control improves with age. A large body of literature has established that there are cognitive processing differences in adolescents (Chuah & Maybery, 1999; Czernochowski et al., 2005; Ferguson & Bowey, 2005; Haselen et al., 2000; Mäntylä et al., 2007; Yuzawa, 2001), and potentially immature cognitive processing contributes to the motor performance differences. Thus, increased experience and developmental changes in brain structure and function may lead to more efficient use of the networks recruited in these tasks (Pangelinan et al., 2011; Thomas et al., 2004).

Another hypothesis suggests adolescents struggle to effectively utilize their internal models to make the necessary feedforward predictions needed to accurately perform a motor action (Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Hay et al., 2005). This inefficiency could be driven by a lack of accurate visuospatial sensory feedback due to a developing central nervous system (CNS), leading to errors when

updating the internal model. So while the sensory feedback at the periphery may be correct, as the information is transmitted through the spinal cord and to the brain, noise is added to the signal. These errors occur not only during and after the movement, but also during planning, as the spatial location of the hand and target are incorrectly programmed. However, adolescents may also have less precise and delayed feedback, meaning that adolescents have less of an ability to detect errors and it takes more time to recognize an error (King et al., 2012).

Alternatively, investigations have suggested that the motor control differences may not be caused by the quality of the sensory feedback but by less experience at interpreting the incoming sensory feedback. For adolescents, the large variety of sensory feedback during a movement (*e.g.* muscle spindle, joint position, visual tracking) could be overwhelming and adolescents may not have developed the correct sensory integration weightings needed to prioritize important sensory information (Goble et al., 2005; Hay et al., 2005; Hay et al., 1991; Redon & Hay, 2005). Further, while the internal models are developing, the ability to perform visuospatial transformations and switch between different parts of the plan may effect an adolescent's ability to perform a motor task (Bo et al., 2006; King et al., 2009). Unfortunately, these hypotheses are primarily driven by behavioral data, which cannot be used to fully identify the underlying neurophysiological differences that are responsible for differential motor performance between adolescents and adults.

Sensorimotor Oscillatory Activity in Adolescents

In addition to the behavioral differences, there are sensorimotor oscillatory activity differences in adolescents. In general, as adolescents develop, the delta and theta oscillations reduce in power, while the alpha and beta oscillations increase in power (Clarke et al., 2001; Pangelinan et al., 2013). When initiating a motor action, adolescents

produce a similar pattern of activity as adults, with some specific differences (Figure 4). The beta ERD in adolescents is delayed compared to adults (Cheyne et al., 2014). The strength of the beta ERD and PMBR change throughout development, along with becoming more lateralized (Gaetz et al., 2010a; Kurz et al., 2016). Adolescents also have activations in other areas of the brain, including the superior temporal gyrus, the cerebellum, and SMA (Cheyne et al., 2014; Wilson et al., 2010). Age related differences have also been seen in the putamen, hippocampus, premotor cortex, inferotemporal cortex, and parietal cortex (Thomas et al., 2004). Moreover, different cortical and subcortical motor systems were recruited by adolescents and adults (Pangelinan et al., 2011; Thomas et al., 2004). Adolescents also exhibited similar patterns to adults in the alpha band, with significant ERD during the execution of a movement (Bender et al., 2004). Despite the recognition that there are developmental differences in this cortical activity, we still have an incomplete understanding of how practicing a motor action relates to these maturational differences in the oscillatory activity.

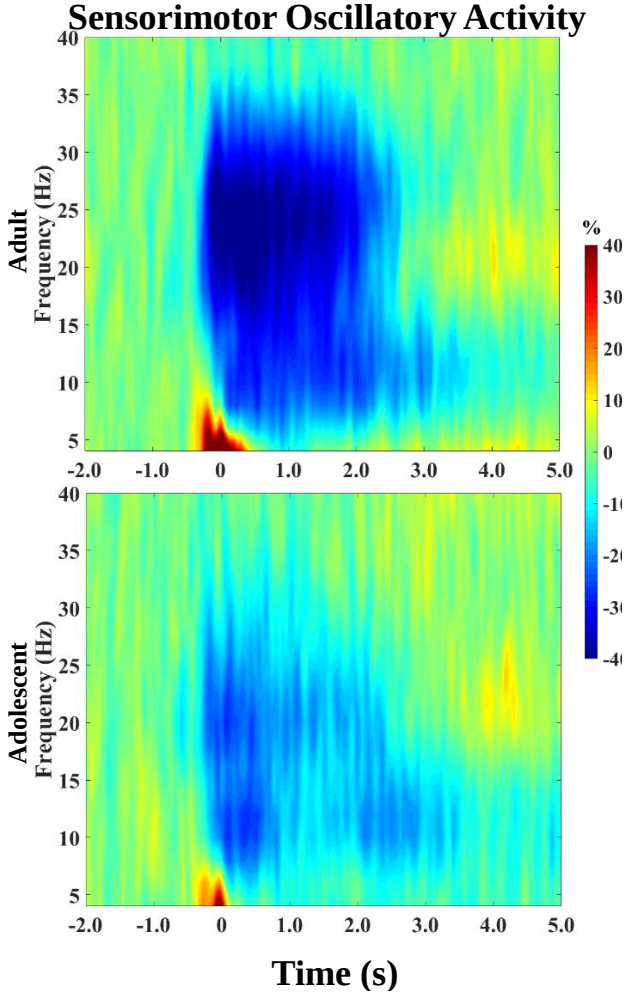

Figure 4: Exemplary Group-averaged time-frequency spectrograms for adolescent and adult groups. Exemplary time-frequency component plots for an MEG sensor above the motor cortices. These are average TFCs for a cohort of A) adults and B) adolescents performing an ankle plantarflexion. Here, the power of the alpha and beta ERD in the adolescent group is weaker.

Motor Learning in Adolescents

In addition to the distinct differences in the sensorimotor oscillatory activity between adults and adolescents, there are differences in the effect of practice between adolescents and adults (Bo et al., 2006; Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Goble et al., 2005; Hay et al., 2005; King et al., 2009; King et al., 2012; Pangelinan et al., 2013; 2011). For adolescents to improve at a level comparable to adults, adolescents require more practice and feedback (Goh et al., 2012; Sullivan et al., 2008). These investigations suggest that adolescents may need more practice time compared to adults in order to reach the same level of performance. Further, adolescents have decreased learning rates and performance compared to adults when given the same amount of training (Thomas et al., 2004). While these practice effect differences are well appreciated, we do not fully understand the neurophysiological nexus for why these differences exists.

Somatosensory Oscillatory Activity in Adolescents

Many of these motor learning differences are thought to be driven in part by somatosensory processing differences. Prior investigations suggest that a somatosensory response comparable to adults is identifiable by about two years of age and continues to develop throughout childhood (Nevalainen et al., 2014; Pihko et al., 2009). By adolescence, the pattern of cortical oscillatory responses to a peripheral stimulus is similar to that in adults, with an immediate broadband ERS followed by an ERD (Dockstader et al., 2009; Dockstader et al., 2008; Kurz et al., 2015; Kurz et al., 2017b, 2018; Wiesman et al., 2017). Furthermore, adolescents also show reduced somatosensory responses when a stimulation occurs during a movement (Kurz et al., 2018). However, whether these cortical oscillations are different between adolescents and adults during movement remains unknown.

Purpose of Dissertation

The first purpose of this dissertation is to begin to address the aforementioned knowledge gaps by quantifying how the cortical oscillatory activity that controls motor actions is different after practicing a motor task. Specifically, this dissertation will compare the alpha and beta ERD power before and after practice to quantify differences in regions of the brain and the distinct stages of the cortical oscillations associated with performing a motor action. It is hypothesized that the power of the beta ERD will be reduced after practice, while there will be no changes in the alpha ERD. Furthermore, it is expected that these changes will be coupled with better performance of the motor task, showing better accuracy, speed, and rate of force production. The outcomes of this primary purpose will establish a baseline to which oscillatory changes in adolescent motor learning can be compared.

The second purpose of this dissertation is to establish how these oscillatory activity power changes differ between adolescents and adults. Specifically, this dissertation will compare the alpha and beta ERD power between adolescents and adults before and after practicing a novel motor task to identify how the cortical oscillations associated with performing a motor action change after practice. It is hypothesized that age group will modulate how the beta ERD changes after practice, while the alpha ERD will be unaffected in either age group. Furthermore, it is expected that the adults will perform the task better, regardless of practice block. The outcomes of this purpose will establish differences in cortical oscillatory activity changes associated with motor learning between adolescents and adults.

The third purpose of this dissertation is to determine if the movement-related attenuation of the somatosensory response is different for adolescents compared to adults. Specifically, this dissertation will compare alpha-beta ERS, gamma ERS, and beta

ERD power attenuations during movement to identify if the magnitude of attenuation is different between adolescents and adults. It is hypothesized that the attenuation of the alpha-beta ERS and beta ERD will be greater in adolescents than in adults. The outcomes of this final purpose will provide insight into the somatosensory processing differences between adolescents and adult, not only during passive stimulation but also when the stimulation occurs during a motor action.

The overall outcome of this dissertation will provide a more complete understanding of the cortical changes that occur during motor learning and how these cortical processes are different in adolescents. This dissertation will provide a new understanding of motor learning differences during adolescents and may be useful for designing motor learning strategies that are more advantageous for younger age groups.

CHAPTER 1: NEUROPHYSIOLOGICAL CHANGES IN THE VISUOMOTOR NETWORK AFTER PRACTICING A MOTOR TASK

INTRODUCTION

It is well recognized that the brain maintains and updates a real time internal representation of how the musculoskeletal system performs under various task constraints (Huang et al., 2011; Hwang & Shadmehr, 2005; Kluzik et al., 2008; Milner & Franklin, 2005; Smith & Shadmehr, 2005; Thoroughman & Shadmehr, 1999). This internal model is used to make feed-forward predictions about the ideal muscle synergies that are necessary to accurately perform a motor task, but these models are rarely perfect and are generally adaptively updated as one becomes more proficient at a motor task (Shadmehr, 2004; Wolpert, 2007). Improving the internal model is thought to be based on sensory feedback and knowledge about the success of the final motor performance (Doyon & Benali, 2005; Willingham, 1998). This process occurs in three distinct stages: 1) a fast motor learning stage where there are rapid improvements in the task performance after a single practice session, 2) a slow motor learning stage where there are incremental improvements across multiple practice sessions, and 3) an offline learning stage where the motor memories are consolidated and skill stabilization occurs (Dayan & Cohen, 2011; Doyon & Benali, 2005; Doyon & Ungerleider, 2002; Fischer et al., 2005; Korman et al., 2003; Muellbacher et al., 2002; Robertson et al., 2004; Walker et al., 2002). While it is accepted that the internal model is updated through these various processing stages, it is not well established how these changes are reflected in the cortical activity of the sensorimotor network.

A few functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) investigations have examined the changes that occur in the internal model of healthy adults after practicing a novel motor task (Arima et al., 2011; Floyer-Lea

& Matthews, 2005; Grafton et al., 2002; Honda et al., 1998; Sacco et al., 2006; 2009; Sakai et al., 1999; Shadmehr & Holcomb, 1997; Zhang et al., 2011). These studies have shown that the strength of activation in the primary motor area, supplementary motor area (SMA), prefrontal cortex, parietal cortex, and the cerebellum can change after practice. The short term changes (e.g., fast motor learning) seen in these cortical areas appear to be associated with improved spatial processing, sensorimotor transformations, online error corrections and improved resource allocation (Doyon & Ungerleider, 2002; Hikosaka et al., 2002; Kelly & Garavan, 2005; Petersen et al., 1998; Tamas Kincses et al., 2008). Although these studies have provided critical insight on the areas of the brain that are altered by practicing a motor task, the role these areas play in the planning and execution of the motor action, and the associated neural dynamics, are not well identified.

Outcomes from electroencephalography (EEG), magnetoencephalography (MEG), and invasive electrocorticography (ECoG) experiments have shown that cortical oscillatory activity decreases in the beta frequency range (15-30 Hz) prior to the onset of movement, and that this is sustained throughout the majority of the movement (Alegre et al., 2002; Cassim et al., 2000; Crone et al., 1998; Heinrichs-Graham & Wilson, 2015; Jurkiewicz et al., 2006; Kaiser et al., 2001; Kilner et al., 2004; Kurz et al., 2017a; Miller et al., 2010; Pfurtscheller & Berghold, 1989; Pfurtscheller et al., 2003; Tzagarakis et al., 2010; Wilson et al., 2014; 2010; 2011). The decrease in the amount of power, commonly termed beta desynchronization, is thought to reflect task-related changes in the activity level of local populations of neurons. The consensus is that this beta event-related desynchronization (ERD) is related to the formulation of a motor plan, because it begins well before the onset of movement and is influenced by the certainty of the movement pattern to be performed (Alegre et al., 2002; Grent-'t-Jong et al., 2014; Heinrichs-Graham & Wilson, 2015; Kaiser et al., 2001; Pollok et al., 2014; Tzagarakis et al., 2010; 2015).

Typical beta ERD responses involve widespread bilateral activity across the sensorimotor cortical areas, with the strongest maxima contralateral to the effector producing the motor action and following the basic homuncular topology of the pre/post central gyri. Additional areas of concurrent beta ERD activity often include the premotor area, SMA, parietal cortices and mid cingulate (Jurkiewicz et al., 2006; Kurz et al., 2016; Tzagarakis et al., 2010; 2015; Wilson et al., 2014). Despite the recognition that beta oscillations play a prominent role in the production of motor actions, we still have an incomplete understanding of how these oscillations are altered after practicing a motor action.

In summary, cortical beta oscillations are known to play a key role in motor planning and execution, but whether these responses are modulated by practice and learning remains largely unknown. Moreover, it is unclear how these cortical oscillations may change across the respective stages of learning (e.g., fast learning, slow learning, and memory consolidation). The objective of the current investigation was to use high-density MEG to begin to address these knowledge gaps by quantifying how beta cortical oscillations during the motor planning and execution stages are altered after a short-term practice session (e.g., fast motor learning stage) involving an ankle plantarflexion motor task.

MATERIAL AND METHODS

Subjects

The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation. Fifteen healthy right-hand dominant adults (Mean Age = 23.3 yrs.; SD: ± 3.3 yrs., 6 female) with no neurological or musculoskeletal impairments participated in this investigation. All of the participants provided written informed consent to participate in the investigation.

MEG Data Acquisition and Experimental Paradigm

Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, the participants were monitored via real-time audio-video feeds from inside the shielded room.

The participants were seated upright in a magnetically-silent chair during the experiment. A custom-built, magnetically-silent force transducer was developed for this investigation to measure isometric ankle plantarflexion forces (Figure 5A). This device consisted of a 20 x 10 cm airbladder that was inflated to 317 kPa, and was integrated within an ankle foot orthosis. Changes in the pressure of the airbag, due to participants' generating an isometric ankle plantarflexion force, were quantified by an air pressure sensor (Phidgets Inc., Calgary, Alberta, CA) and were converted into units of force offline.

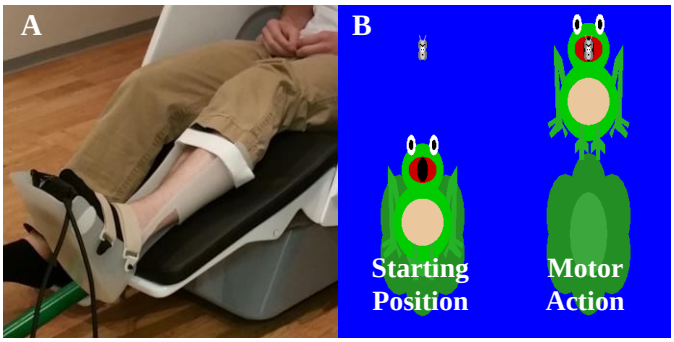

Figure 5: Participant in MEG Chair with Pneumatic Device on Leg and Visual Presentation. A) Participant seated in the MEG chair with the custom pneumatic ankle force system on their left leg. The device consists of an airbag that is encased in a ridged ankle-foot orthotic. B) Visual feedback displayed to the participant. Ankle plantarflexion forces generated by the participant animated the vertical position of a frog's position on the screen. A successful trial occurred when the participant generated a plantarflexion force that positioned the frog's mouth at the bug's position and held it there for 300 ms. (Gehringer et al., 2018).

The experimental paradigm involved the participant generating an isometric ankle plantarflexion force with their left leg that matched target forces that varied between 15-30% of the participant's maximum isometric ankle plantarflexion force. The step size between the respective targets was one unit of force. The target force was visually displayed as a moth and the force generated by the participant was shown as a frog that

was animated vertically, based on the isometric force generated (Figure 5B). The participants were instructed to match the presented targets as fast and as accurately as possible. The distinct target forces were presented in a random order, and a successful match occurred when the bug that represented the target force was inside of the frog's mouth for 0.3 s. The stimuli were shown on a back-projection screen that was approximately ~1 meter in front of the participant and at eye-level. Each trial was 10 s in length. The participants started each trial at rest while fixated at the center of the screen for 5 s. After this rest period, the target would appear, prompting the participant to try and produce the matching force value. The target was available to be matched for up to 5 s. Once the target was matched or 5 s elapsed, feedback was given to indicate the end of the trial, and the participant returned to rest and fixated on the center of the screen while waiting for the next target to appear. Participants performed three blocks of the ankle plantarflexion target-matching task, with each block containing 100 trials and up to 3 minutes between each block. The first and third blocks were performed while recording MEG data, while the second block acted as an extended practice block, where the participant was provided additional information about the accuracy of their target matching performance via an interactive biofeedback program. This program showed the participant the amount of error in their motor action by displaying the distance between the bug and the frog, and provided auditory and visual rewards when the participant matched the target faster and had improved accuracy.

MEG Coregistration

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Prior to the experiment, the location of these coils, three fiducial points and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with

a unique frequency label (*e.g.*, 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed for each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered to a template structural MRI and transformed into native space using three external landmarks (*i.e.*, fiducials), and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

MEG Pre-Processing, Time-Frequency Transformation, & Statistics

Using the MaxFilter software (Elekta), each MEG data set was individually corrected for head motion that may have occurred during task performance, and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. The continuous magnetic time series was divided into epochs of 10.0 s in duration (-5.0 s to +5.0 s), with the onset of the isometric force defined as 0.0 s and the baseline defined as -2.0 to -1.4 s. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation (resolution: 2.0 Hz, 0.025 s) and averaged over the respective trials. These sensor-level data were normalized by dividing the power value of each time-frequency bin by the respective bin's baseline power, which was calculated as the mean power during the baseline (−2.0 to -1.4 s). This time window was selected for the baseline based on our inspection of the sensor level absolute power data, which showed that this time window was quiet and temporally distant from the peri-movement oscillatory activity. The specific time-frequency windows used for imaging were determined by statistical analysis of the

sensor-level spectrograms across the entire array of gradiometers. Briefly, each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point and the output spectrogram of t-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants and conditions. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the ($p < 0.05$) threshold, and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris & Oostenveld, 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

MEG Source Imaging

A minimum variance vector beamforming algorithm was employed to calculate the source power across the entire brain volume (Gross et al., 2001). The single images were derived from the cross spectral densities of all combinations of MEG sensors and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images were normalized per subject using a separately averaged pre-stimulus noise period of equal duration (-2.0 to -1.4 s) and bandwidth (Alpha: 8 – 14 Hz, Beta: 24 – 32 Hz) (Hillebrand & Barnes, 2005; Hillebrand et al., 2005; Van Veen et al., 1997). Thus, the normalized power per voxel was computed over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. Each participant's functional images, which were co-registered to anatomical images prior to

beamforming, were transformed into standardized space using the transform previously applied to the structural MRI volume and spatially resampled. MEG pre-processing and imaging used the Brain Electrical Source Analysis (BESA) software (BESA v6.0; Grafelfing, Germany).

Time series analysis was subsequently performed on the peak voxels extracted from the group-averaged beamformer images (see Results below). The virtual sensors were created by applying the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which resulted in a time series with the same temporal resolution as the original MEG recording (Cheyne et al., 2006; Heinrichs-Graham et al., 2016; Heinrichs-Graham & Wilson, 2016). Once the virtual sensors were extracted, they were transformed into the time-frequency domain and the two orientations for each peak voxel per individual were combined using a vector-summing algorithm. The power of these time courses, relative to baseline, was averaged across the window of interest for each individual to assess the temporal evolution of the key oscillatory responses. The post-movement beta responses were not examined because we had no hypotheses about these, and because there were significant behavioral differences between pre- and post-practice which would have biased any analyses.

Motor Behavioral Data

The output of the force transducer was simultaneously collected at 1 kHz along with the MEG data, and was used to quantify the participant's motor performance. The formulation of the motor plan was assumed to be represented by the participant's reaction time, which was calculated based on the time from when the target was presented to when force production was initiated. The amount of error in the feedforward execution of the motor plan was behaviorally quantified based on the percent overshoot of the target. The time to match the target was used to quantify the online corrections that were made after the initial motor plan was executed. The online corrections were calculated based on the

time difference between the reaction time and the time to reach the target. The coefficient of variation in the force produced while attempting to match the target was also used to evaluate the online corrections that the participants made while trying to match the target. A lower coefficient of variation signified fewer corrections in the force production when attempting to match the target. Paired-samples t-tests at a 0.05 alpha level were used to determine if there were differences in the behavioral performance of the participants between the pre- and post-practice blocks. Pearson's correlations were ran to assess the relationship between the percent change in the averaged time series data and the motor performance.

RESULTS

Motor Behavioral Results

Overall, our results showed that the participants improved their ability to predict the ankle forces that would accurately match the prescribed targets (Figure 6). After practicing, the participants matched the targets faster (P = 0.003), had less errors in their force production (P = 0.02), had a faster velocity of the force production towards the target (P = 0.007), and a lower coefficient of variation when attempting to match the target (P = 0.011). There was no differences in the reaction time after practicing (P = 0.19). Time to

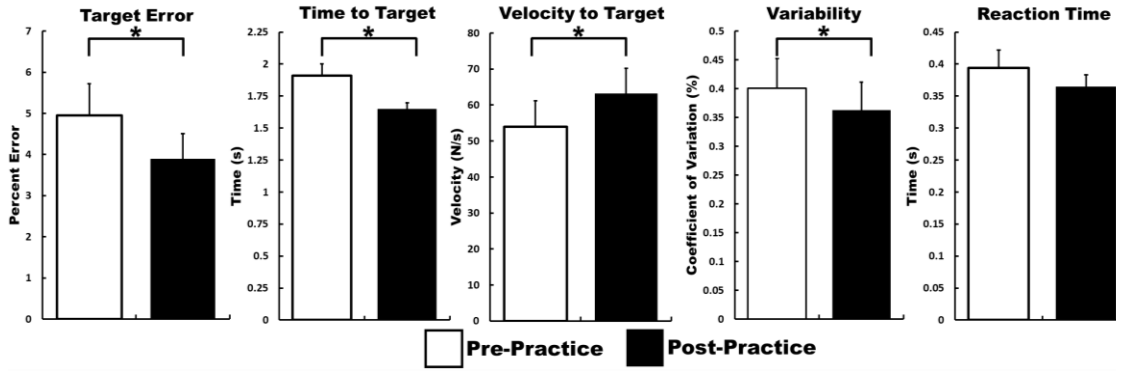

Figure 6: Changes in behavioral measurements. White represents the pre-practice block while black represents the post-practice block (Gehringer et al., 2018).

match the target showed a large effect size (d = 0.86), while target error (d = 0.39), velocity (d = 0.34), and variability (d = 0.20) showed small to moderate effects.

Sensor-Level Results

When collapsing the data across the respective blocks (pre- and post-practice), there were significant alpha (8-14 Hz) and beta (24-32 Hz) ERDs that were present in a large number of sensors near the fronto-parietal region (P < 0.0001, corrected). These responses in the alpha band started near movement onset (0.0 s) and were sustained for approximately 0.6 s afterward (Figure 7). The responses in the beta band started about 0.3 s before movement onset and were sustained for approximately 0.6 s afterward (Figure 7). For illustrative purposes, we show the pre and post practice time frequency plots in Figure 7, but note that sensor-based statistics were computed by collapsing the data across the pre- and post-practice blocks. Qualitative inspection of these figures

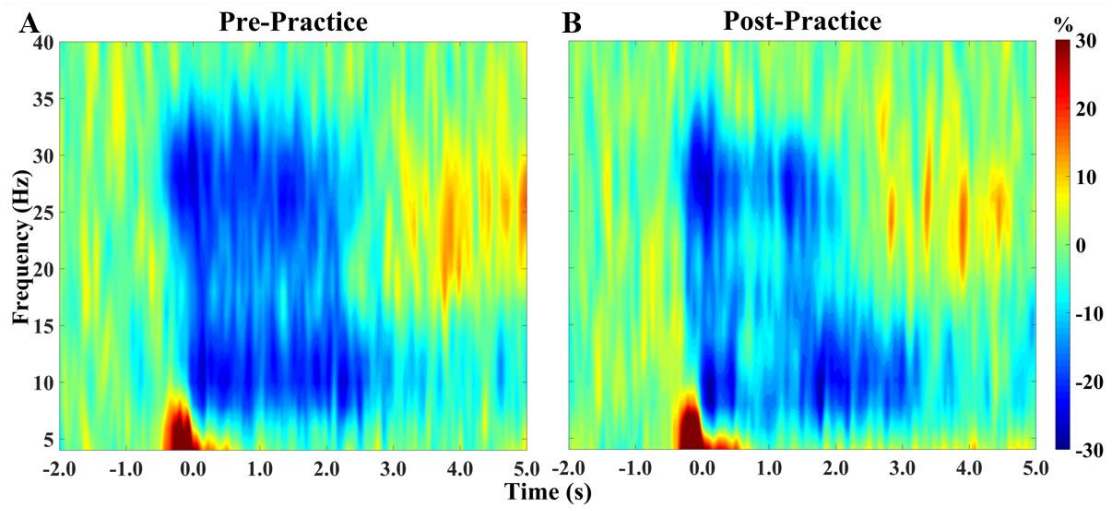

Figure 7: Group averaged time-frequency spectrograms for pre- and post-practice blocks. Group averaged time-frequency spectrograms for pre- (A) and post-practice (B) blocks. Frequency (Hz) is shown on the y-axis and time (s) is denoted on the x-axis, with 0 s defined as movement onset. The event-related spectral changes during the ankle plantarflexion target-matching task are expressed as percent difference from baseline (−2.0 to -1.4 s). The MEG gradiometer with the greatest response amplitude was located near the medial primary sensorimotor cortices, contralateral to the ankle used during the task. There was a strong desynchronization in the alpha (8 – 14 Hz) and beta (24 – 32 Hz) bands in both the pre- and post-practice blocks. As can be discerned, the strength of the alpha and beta desynchronization became notably weaker in the post-practice MEG session. The color scale bar for both plots is shown to the far right (Gehringer et al., 2018).

shows that the strength of the alpha and beta ERDs appeared to become weaker after practice.

Alpha Oscillations

The alpha (8-14 Hz) ERD identified in the sensor-level analysis within the 0.0 to 0.6 s time window was imaged using a beamformer. This analysis combined the MEG data acquired across the respective blocks, and used a baseline period of −2.0 to -1.4 s. The resulting images were grand-averaged and revealed that the alpha ERD response was generated by parietal and occipital cortices (Figure 4). The local maximums seen in these cortical areas were subsequently used as seeds for extracting virtual sensor time courses (i.e., voxel time courses) from the pre and post-practice block images. Peaks were found in the left parietal cortex and

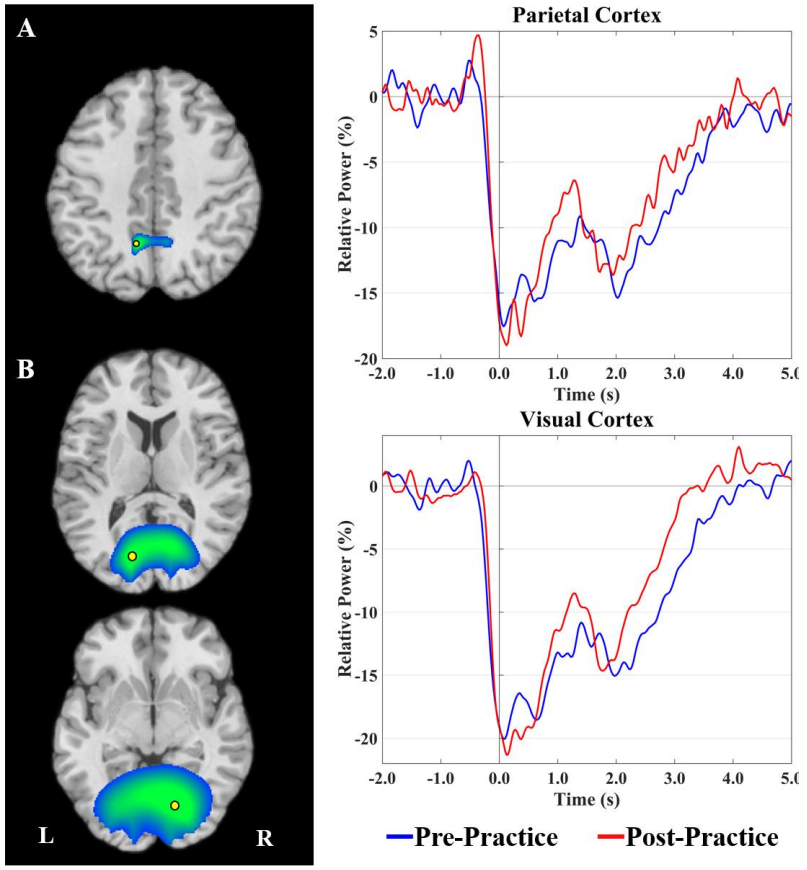

Figure 8: Grand averaged beamformer images and time series of alpha activity in the parietal and occipital cortices. Grand averaged beamformer images of alpha activity (8-14 Hz) from -0.0 to 0.6 s revealed two main clusters in the parietal (A) and occipital cortices (B). Time series data were extracted from the peak voxel in these clusters (yellow markers) and are plotted with power changes relative to the baseline shown in a percent scale on the y-axis and time on the x-axis in seconds. Bilateral peaks were found in the occipital cortex, and were averaged to create a single time series. There were no pre/post-practice differences in the alpha event-related desynchronization (ERD) during motor execution (0 – 0.6 s) in the parietal and occipital cortices. Note that we did not examine the post-movement alpha responses because we had no hypotheses about these, and because there were significant behavioral differences between pre- and post-practice which would have biased any analyses. (Gehringer et al., 2018).

bilaterally in the occipital. As the target-matching task was not designed to interrogate hemispheric effects, the two occipital peaks were averaged to create a single time series. Separate paired samples t-tests were conducted to determine if the average virtual sensor activity during the motor execution stage (0 to 0.6 s) changed after practice in the parietal and occipital cortices. Note that we did not examine the post-movement beta responses (> 0.6 s) because there were significant behavioral differences between pre- and post-practice which would have biased any analyses.

For the left parietal cortex, there was no significant difference in the alpha ERD response indicating that it was not affected by practice (P = 0.31, Figure 4A). The results for the occipital cortices were similar, as there were no differences in the alpha ERD after practice (P = 0.33, Figure 4B). Hence, the alpha ERD in the left parietal and bilateral occipital cortices were not affected by practice.

Beta Oscillations

The beta (24-32 Hz) ERD identified in the sensor-level analysis between -0.3 and 0.3 s was imaged using a beamformer. As with the alpha response, this analysis combined the data acquired across the respective blocks, and used a baseline period of −2.0 to -1.4 s. The resulting images indicated that the beta ERD was more centered on the leg region of the sensorimotor cortices, with additional clusters seen in the occipital cortices (Figure 5). The local maximums of these responses were next used as seeds for extracting virtual sensors from the pre and post-practice data blocks separately. Peaks were found in the leg region of the sensorimotor strip, and bilaterally in the occipital cortices. As with the alpha data, the two occipital peaks were averaged to create a single time series since the paradigm was not designed to interrogate hemispheric effects. Since the beta response extended across movement onset (i.e., 0.0 s), we conducted separate repeated measures

ANOVAs (pre/post-practice block X Time Window) to determine if the average neural activity during the motor planning (-0.3 to 0 s) and execution stages (0 to 0.3 s) changed after practice in the right sensorimotor and bilateral occipital cortices. Note that we did not examine the post-movement beta responses (> 0.6 s) because there were significant behavioral differences between pre- and post-practice which would have biased any analyses.

For the right sensorimotor cortices, there was no main effect of time window (*P* = 0.13), which suggests that the strength of the beta ERD was roughly equivalent across the motor planning and execution stages. However, there was a significant pre/post practice main effect (*P* = 0.03), revealing that the beta ERD was significantly weaker overall after practice (Figure 5A). The

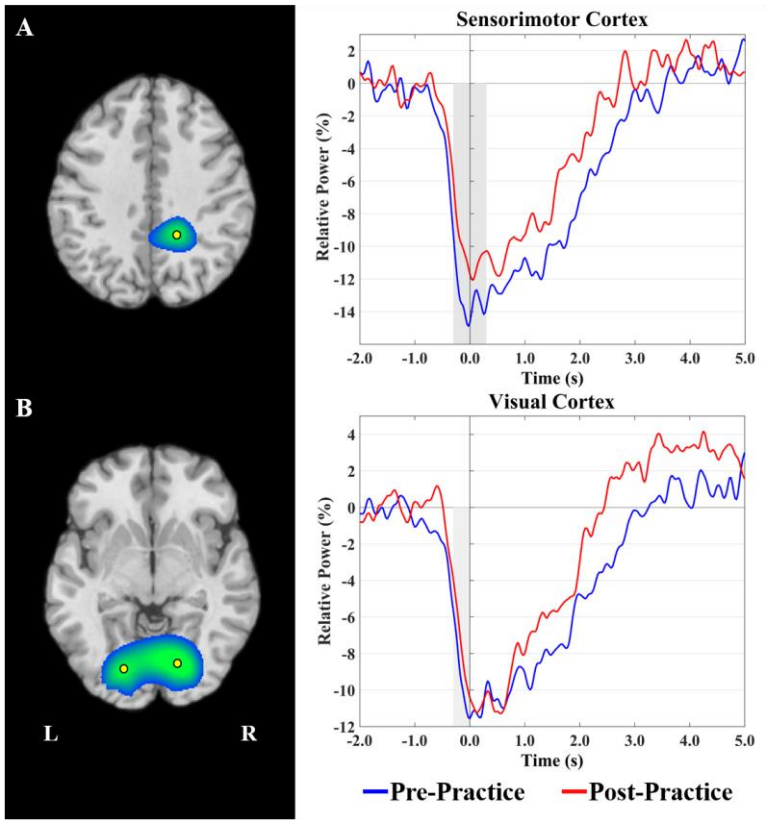

Figure 9: Grand averaged beamformer images and time series of beta activity in the sensorimotor and occipital cortices. Grand averaged beamformer images of beta activity (24-32 Hz) from -0.3 to 0.3 s revealed two main clusters in the sensorimotor (A) and occipital cortices (B). Time series data were extracted from the peak voxel in these clusters (yellow markers), and are plotted as in Figure 4. Bilateral peaks were found in the occipital cortex, and were averaged to create a single time series. There was significantly weaker beta event-related desychronication (ERD) in the sensorimotor cortex during the motor planning (-0.3 – 0s) and execution (0 – 0.3s) stages after practice. There was also significantly weaker beta ERD in the visual cortex during the motor planning stage (-0.3 – 0s) after practice. No differences were detected during the motor execution window (0 to 0.3s) in the visual cortex. Significant power differences are denoted by the gray shading. Note that we did not examine the post-movement beta responses because we had no hypotheses about these, and because there were significant behavioral differences between pre- and post-practice which would have biased any analyses (Gehringer et al., 2018).

interaction term was not significant ($P = 0.25$).

For the occipital cortices, there was a significant main effect of time window ($P < 0.01$), indicating the power of the beta ERD in the occipital cortices was weaker during motor planning compared to the motor execution stage. There was no pre/post-practice main effect ($P = 0.14$). However, the interaction term was significant ($P = 0.05$), and our follow-up post hoc analyses showed that the beta ERD was significantly weaker in the occipital cortices during the motor planning stage after practice ($P = 0.05$, Figure 5B).

Correlational Results

The changes in the alpha and beta ERDs after practice were not related to the changes in any of the five motor behavioral outcomes (Ps > 0.05).

DISCUSSION

There is currently a substantial knowledge gap in our understanding of how the cortical oscillations are altered after practicing a novel motor task. The current study used high-density MEG to begin to fill this knowledge gap by quantifying changes in the cortical oscillations after a short-term practice (e.g., fast-motor learning) session of a goal-directed, isometric, target-matching ankle plantarflexion task. At the onset of this investigation, we were primarily driven to identify the potential differences in beta cortical oscillations, since these oscillations are widely-known to be involved in the planning and execution of motor actions (Grent-'t-Jong et al., 2014; Heinrichs-Graham & Wilson, 2015; Kurz et al., 2014a; 2016; Pollok et al., 2014; Tzagarakis et al., 2010; 2015). However, the data driven approach employed in this investigation revealed that there were notable differences in both alpha and beta oscillatory activity during the planning and execution of isometric force. Thus, we examined both using our beamforming approach, but in the end our results showed that only the beta cortical oscillations changed after practicing the motor task. These results imply that changes in the strength of beta oscillations are likely

central to the noted improvements seen in the accuracy and speed of the participant's motor performance after practice. Alternatively, these results could be a single part of a larger change in the visuomotor network as a whole.

Our results showed that the strength of the beta ERD in the leg region of the sensorimotor cortices across the motor planning and execution stages became significantly weaker after practicing the motor task. These results concur with previous fMRI, EEG, and PET investigations that have shown that activation changes primarily reside in the sensorimotor network after practicing a novel motor task (Classen et al., 1998; Galea & Celnik, 2009; Galea et al., 2011; Hadipour-Niktarash et al., 2007; Hatfield et al., 2004; Haufler et al., 2000; Hillman et al., 2000; Kranczioch et al., 2008; Orban de Xivry et al., 2011; Reis et al., 2009; Zhang et al., 2011). Another common finding is that the size of the activation in the motor cortex decreases after practice (Floyer-Lea & Matthews, 2004; Karni et al., 1995; Kelly & Garavan, 2005; Petersen et al., 1998; Poldrack, 2000). Such reductions in sensorimotor activation, which have been demonstrated over a single practice session (Karni et al., 1995), suggests that less cognitive and/or neural resources are required to successfully preform the task (Kelly & Garavan, 2005; Petersen et al., 1998; Poldrack, 2000). Potentially, the weaker beta cortical oscillations seen in this investigation might also represent a consolidation of the cortical resources that are necessary for performing the ankle plantarflexion target matching task.

Practice was also associated with a reduction in the strength of the beta ERD within the occipital cortices during the motor planning stage after practice. Prior studies have implied that the occipital cortices contribute to the visuomotor transformations that are necessary for planning a motor action that will match the prescribed target location (Krigolson et al., 2015; Kurz et al., 2017a; Messier & Kalaska, 1997; Shadmehr & Mussa-Ivaldi, 1994). Hence, we suspect that the weaker beta ERD seen in our study after practice

might reflect an improvement in the cortical resources that are needed to compute the transformations that are necessary between the visual representation of the target and the ankle plantarflexion force. Alternatively, the weaker beta ERD could suggest that the weighting of the visual feedback was reduced after practice. This logic is based on previous work that has suggested the weightings of the visual and proprioceptive feedback changes as learning occurs, and that the change in the balance between these two sensory modalities is dependent on the task constraints (Sober & Sabes, 2003, 2005).

Our analysis also identified an alpha ERD in parietal and occipital cortices that was present across the motor planning and execution stages. The location and timing of these neural oscillations are aligned with the breadth of literature that suggests that activity within these cortical areas is associated with the visuomotor transformations that are necessary for producing and correcting a motor action (Beurze et al., 2007; Buneo & Andersen, 2006; Della-Maggiore et al., 2004; 2013; Gallivan et al., 2011; Kurz et al., 2016; Valyear & Frey, 2015). Nevertheless, the results of the current experiment imply that motor-related alpha oscillations do not appreciably change after short-term practice. These results are somewhat perplexing since prior MEG and EEG studies have noted that alpha oscillations in sensors near the sensorimotor cortices became weaker after practicing a motor sequence with the fingers (Leocani et al., 1997; Pollok et al., 2014). We speculate that these discrepancies might reside in the differences between implicit and explicit learning. The finger motor action sequence learned in these previous studies were acquired implicitly, while the ankle motor action learned in this investigation was acquired explicitly. However, while this explanation is conceivable, it needs to be experimentally challenged before it can be fully supported.

Our understanding of the brain networks that serve the planning and execution of motor actions is largely based on experiments with the upper extremities. In fact, there is a vast knowledge gap surrounding the neural regions that are involved in the production

of leg motor actions. Studying leg motor actions has historically been more difficult due to the increased probability of head movements, the greater chance of artifacts resulting from the movement of the large leg mass within the MRI scanner's magnetic field, and the challenge of building magnetically silent devices that can be used to concurrently measure the biomechanics of the leg motor actions while in a supine position (Barry et al., 2010; Seto et al., 2001). Outcomes from the few investigations that have been conducted have shown that the production of self-paced toe, ankle, and knee motor actions arise from the same cortical and subcortical structures seen in the prior upper extremity experiments, but emanate from different neural populations following the homuncular map within each structure (Ciccarelli et al., 2005; de Almeida et al., 2015; Dobkin et al., 2004; Johannsen et al., 2001; Kapreli et al., 2006; Luft et al., 2002). However, beyond this anatomical information, we still have limited understanding of how these cortical areas are involved in the planning and production of leg motor actions. The results from this study align with the few MEG studies that have been conducted on the leg motor actions (Arpin et al., 2017; Kurz et al., 2014a; 2016; 2017a). In addition, our investigation has extended the outcomes from these few studies by showing that the strength of beta cortical oscillations within the sensorimotor and occipital cortices becomes weaker after practicing an isometric ankle plantarflexion target matching task. These results further emphasize that the beta cortical oscillations seen during the motor planning and execution stages play a prominent role in the control of the leg motor actions.

The outcomes presented in this study apply to the fast-motor learning stage where there are rapid improvements in task performance after a single session of practice, and much less to learning that occurs gradually over a longer period of time with intermittent practice sessions. Further studies are warranted to evaluate if beta cortical oscillations also play a prominent role in the motor behavioral improvements seen across such multiple practice sessions, and their role in the formulation of long-term motor memories.

These insights may augment the development of neurologically based practice strategies that can improve the ability of individuals to master novel motor skills. Additionally, the results presented in this study showed no relationship between the changes in the motor performance and the oscillatory activity. This may suggest that the changes in the visuomotor network may be a part of a change in the overall motor network. Motor learning involves interactions between the visuomotor networks, subcortical structures, like the basal ganglia and cerebellum, and the spinal cord (Doya, 2000; Doyon & Benali, 2005; Doyon & Ungerleider, 2002; Hikosaka et al., 2002; Seger, 2006; Vahdat et al., 2015). Changes that occur in the subcortical regions and spinal cord may be linked with the changes in motor performance but further investigation would be needed to fully determine this relationship.

CONCLUSIONS

Fast-motor learning results in a reduced amount of power in the beta ERD seen in the sensorimotor and visual cortices. These changes likely reflect the reduction in neuronal resources needed to perform a motor action. Alternatively, the changes in the visual cortices during the planning phase may reflect a reduction of the weighting of visual information. The beta ERD changes were concurrent with improvements in task performance, which indicate these cortical changes reflect fast motor learning.

CHAPTER 2: PRACTICE MODULATES MOTOR-RELATED BETA OSCILLATIONS DIFFERENTLY IN ADOLESCENTS AND ADULTS

INTRODUCTION

It is well recognized that the brain maintains and updates a real-time internal representation of how the musculoskeletal system performs under various task constraints (Huang et al., 2011; Hwang & Shadmehr, 2005; Kluzik et al., 2008; Milner & Franklin, 2005; Smith & Shadmehr, 2005; Thoroughman & Shadmehr, 1999). This internal model is used to make feed-forward predictions about the ideal muscle synergies that are necessary to accurately perform a motor task, but these models are rarely perfect (Shadmehr, 2004; Wolpert, 2007). Improving the internal model through practice is based on the sensory feedback, and knowledge about the success of the final motor performance (Doyon & Benali, 2005; Willingham, 1998). While it is accepted that the internal model is updated in both adults and adolescents, there are differences in the effect of practice between adolescents and adults (Bo et al., 2006; Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Goble et al., 2005; Hay et al., 2005; King et al., 2009; King et al., 2012; Pangelinan et al., 2013; 2011). For adolescents to improve at a level comparable to adults, adolescents require more practice and feedback (Goh et al., 2012; Sullivan et al., 2008). While these practice effect differences are well appreciated, we do not fully understand the neurophysiological nexus for why these differences exists.

A large body of literature has established that there are cognitive processing differences in adolescents (Chuah & Maybery, 1999; Czernochowski et al., 2005; Ferguson & Bowey, 2005; Haselen et al., 2000; Mäntylä et al., 2007; Yuzawa, 2001), and potentially immature cognitive processing contributes to the motor performance differences. It has been hypothesized that these motor performance differences may simply arise from inexperience with the task and may improve with practice (Contreras-

Vidal, 2006; 2005; Goble et al., 2005; King et al., 2009; 2012; Pangelinan et al., 2013; 2011). It has also been hypothesized that inexperience may lead to difficulty switching between relevant alternative motor plans and/or greater reliance on online error corrections, as opposed to selecting an appropriate motor plan initially (Bo et al., 2006; Hay et al., 2005). Furthermore, this inexperience may lead to suboptimal updates to the internal model (Goble et al., 2005). Collectively, these hypotheses suggest that the adolescent brain is less efficient at executing motor plans and interpreting the feedback sensory information that returns during and upon the completion of the motor task. Unfortunately, these hypotheses are primarily driven by behavioral data, which cannot be used to fully identify the underlying neurophysiological differences that are responsible for differential motor performance between adolescents and adults.

In adults, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) investigations have examined the neural changes that occur after practicing a novel motor task (Arima et al., 2011; Floyer-Lea & Matthews, 2005; Gehringer et al., 2018; Grafton et al., 2002; Rueda-Delgado et al., 2014; Sacco et al., 2006; 2009; Shadmehr & Holcomb, 1997; van Wijk et al., 2012; Zhang et al., 2011). These studies, focusing mainly on upper extremity motor tasks, have shown that the primary motor area, supplementary motor area, prefrontal cortex, and parietal cortex exhibit changes in the strength of activation after participants practice. The short-term changes seen in these cortical areas have been associated with improved spatial processing, sensorimotor transformations, online error corrections and improved resource allocation (Boonstra et al., 2007; Doyon & Ungerleider, 2002; Gehringer et al., 2018; Hikosaka et al., 2002; Houweling et al., 2008; Kelly & Garavan, 2005; Petersen et al., 1998; Tamas Kincses et al., 2008). Although this work has provided pertinent results demonstrating differences in the how cortical activity changes after practice, the roles that

these cortical areas play in the planning and execution of a lower extremity motor action after practice have not been identified, especially in adolescents.

Outcomes from electroencephalography (EEG), MEG, and invasive electrocorticography (ECoG) experiments have shown that prior to the onset of movement the cortical oscillatory activity in the beta frequency range (15-30 Hz) decreases, and this change is sustained throughout the majority of the movement (Deecke et al., 1983; Gehringer et al., 2018; Heinrichs-Graham & Wilson, 2015; Jurkiewicz et al., 2006; Kilner et al., 2004; Kurz et al., 2017a; Miller et al., 2010; Pfurtscheller et al., 2003; Tzagarakis et al., 2010; Wilson et al., 2014; 2010; 2011). This decreased power within the beta frequency band, commonly termed beta desynchronization, is thought to reflect task-related changes in oscillatory activity within local populations of neurons, as they begin to prepare for the specific demands of the pending motor action. The consensus is that this beta event-related desynchronization (ERD) is related to the formulation of a motor plan, because it occurs well before the onset of movement and is influenced by the certainty of the movement pattern to be performed (Grent-'t-Jong et al., 2014; Heinrichs-Graham & Wilson, 2015; Pollok et al., 2014; Tzagarakis et al., 2010; 2015). Typical beta ERD responses involve widespread bilateral activity across the fronto-parietal cortical areas, with the strongest maxima contralateral to the effector producing the motor action and following the basic homuncular topology seen in the pre/postcentral gyrus. Additional areas of concurrent beta ERD activity often include the premotor area, SMA, parietal cortices and mid cingulate (Jurkiewicz et al., 2006; Kurz et al., 2016; Tzagarakis et al., 2010; 2015; Wilson et al., 2014). This pattern of activity has also been observed in adolescents but with distinct differences (Cheyne et al., 2014; Gaetz et al., 2010a; Kurz et al., 2016; Wilson et al., 2010). The strength of the beta ERD in adolescents is weaker compared to adults (Gaetz et al., 2010a). In addition, adolescents also demonstrate

activations in additional areas of the brain, suggesting maturation has an effect on the recruited areas of the sensorimotor network (Kurz et al., 2016; Wilson et al., 2010). Despite the recognition that there are developmental differences in this cortical activity, we still have an incomplete understanding of how practicing a motor action relates to these maturational differences in the oscillatory activity.

Overall, there are clear gaps in the scientific literature regarding the impact of practicing a motor task on cortical beta oscillations in adolescents. Moreover, it is unclear how these cortical oscillations may change after practice. The objective of the current investigation was to use high-density MEG to identify how practicing an ankle plantarflexion target matching task differentially affects motor-related beta oscillations in adults and adolescents.

MATERIAL AND METHODS

Subjects

The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation. Forty-three subjects with no neurological or musculoskeletal impairments participated in this investigation, with twenty-two being healthy right-hand dominant adults (Mean Age = 36.6 yrs.; SD: ± 5.0 yrs., 12 female) and twenty-one being healthy right-hand dominant adolescents (Mean Age = 14.0 yrs.; SD: ± 2.1 yrs., 9 female). All of the participants or guardians provided written informed consent and the adolescents provided assent to participate in the investigation.

MEG Data Acquisition and Experimental Paradigm

Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. All

recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, the participants were seated upright in a magnetically-silent chair and monitored via real-time audio-video feeds from inside the shielded room during the experiment.

A custom-built, magnetically-silent force transducer was developed for this investigation to measure isometric ankle plantarflexion forces (Figure 10A). This device consisted of a 20 x 10 cm air bladder that was inflated to 317 kPa and was integrated within an ankle foot orthosis. Changes in the pressure of the airbag, due to participants' generating an isometric ankle plantarflexion force, were quantified by an air pressure sensor (Phidgets Inc., Calgary, Alberta, CA) and were converted into units of force offline.

The experimental paradigm involved the participant generating an isometric ankle plantarflexion force with their right leg that matched target forces that varied between 15-30% of the participant's maximum isometric ankle plantarflexion force. The step size between the respective targets was one unit of force. The target force was visually displayed as a moth, and the force generated by the participant was shown as a frog that was animated vertically, based on the isometric force generated (Figure 10B). The participants were instructed to match the presented targets as fast and as accurately as possible. The distinct target forces were presented in a random order, and a successful match occurred when the bug that represented the target force was inside the frog's mouth for 0.3 s. The stimuli were shown on a back-projection

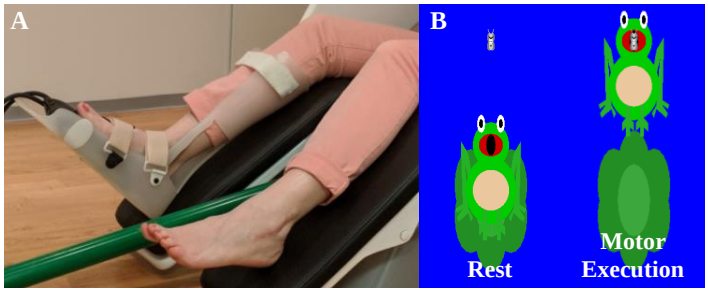

Figure 10: Participant seated in the MEG chair with the custom pneumatic ankle force system on their right leg and visual stimulus. A) Participant seated in the MEG chair with the custom pneumatic ankle force system on their right leg. The device consists of an airbag that is encased in a ridged ankle-foot orthotic. B) Visual feedback displayed to the participant. Ankle plantarflexion forces generated by the participant animated the vertical position of a frog on the screen. A successful trial occurred when the participant generated a plantarflexion force that positioned the frog's mouth at the bug's position and held it there for 0.3 s.

screen that was approximately ~1 meter in front of the participant and at eye-level. Each trial was 10 s in length. The participants started each trial at rest while fixating the center of the screen for 5 s. After this rest period, the target would appear, prompting the participant to try and produce the matching force value. The target was available to be matched for up to 5 s. Once the target was matched or 5 s elapsed, feedback was given to indicate the end of the trial, and the participant returned to rest and fixated on the center of the screen while waiting for the next target to appear. Participants performed three blocks of the ankle plantarflexion target-matching task, with each block containing 100 trials. The first and third blocks were performed while recording MEG data, while the second block acted as an extended practice block, where the participant was provided additional information about the accuracy of their target matching performance via an interactive biofeedback program. This program showed the participant the amount of error in their motor action by displaying the distance between the bug and the frog and provided auditory and visual rewards when the participant matched the target faster and had improved accuracy.

MEG Coregistration

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (*e.g.*, 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed for each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common

coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered to a structural MRI (MPRAGE) using three external landmarks (*i.e.*, fiducials), and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures, and all data were transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

MEG Pre-Processing, Time-Frequency Transformation, & Statistics

Using the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion that may have occurred during the task performance, and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. Essentially, trials that had large gradient or amplitude values (such as those arising from muscular activity in the neck or shoulders) of the magnetic time series were removed prior to time-frequency decomposition. The continuous magnetic time series was divided into epochs of 10.0 s in duration (-5.0 s to +5.0 s), with the onset of the isometric force defined as 0.0 s and the baseline defined as -2.0 to -1.4 s. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation (resolution: 2.0 Hz, 0.025 s) and averaged over the respective trials. These sensor-level data were normalized using the respective bin's baseline power, which was calculated as the mean power during the baseline (−2.0 to -1.4 s). This time window was selected for the baseline based on our inspection of the sensor level absolute power data, which showed that this time window was quiet and temporally distant from the peri-movement oscillatory activity. The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Briefly, each data point in the

spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point, and the output spectrogram of t-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants and conditions. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also below the ($p < 0.05$) threshold and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values, and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris & Oostenveld, 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

MEG Source Imaging

A minimum variance vector beamforming algorithm was employed to calculate the source power across the entire brain volume (Gross et al., 2001). The single images were derived from the cross spectral densities of all combinations of MEG sensors and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth to the target periods that were identified through the sensor-level statistical analyses (see above; Hillebrand & Barnes, 2005; Hillebrand et al., 2005; Van Veen et al., 1997). Thus, the normalized power per voxel was computed over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. MEG pre-processing and imaging used the Brain Electrical

Source Analysis (BESA) software (BESA v6.0; Grafelfing, Germany).

Time series analysis was subsequently performed on the peak voxels extracted from the grand-averaged beamformer images (see Results). The virtual sensors were created by applying the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which resulted in a time series with the same temporal resolution as the original MEG recording (Cheyne et al., 2006; Heinrichs-Graham et al., 2016; Heinrichs-Graham & Wilson, 2016). Once the virtual sensors were extracted, they were transformed into the time-frequency domain, and the two orientations for each peak voxel per individual were combined using a vector-summing algorithm. The power of these time courses, relative to baseline, was averaged across the window of interest for each individual to assess group and practice differences in the key oscillatory responses. A 2x2x2 repeated measures ANOVA (pre/post-practice X adolescent/adult X planning/execution) at a 0.05 alpha level were used to determine if there were differences in average beta power, and a repeated measures 2x2 ANOVA (pre/post-practice X adolescent/adult) at a 0.05 alpha level were used to determine if there were differences in the average alpha power. The post-movement beta rebound responses were not examined because there were significant pre-/post-practice differences in the time that the participants took to match the target, which would have confounded the analyses.

Motor Behavioral Data

The output of the force transducer was simultaneously collected at 1 kHz along with the MEG data and was used to quantify the participant's motor performance. The formulation of the motor plan was assumed to be represented by the participant's reaction time, which was calculated based on the time from when the target was presented to when force production was initiated. The amount of error in the feedforward execution of the motor plan was behaviorally quantified based on the percent overshoot of the target. The

time to match the target was used to quantify the online corrections that were made after the initial motor plan was executed. The online corrections were calculated based on the time difference between the reaction time and the time to reach the target. The coefficient of variation in the force produced while attempting to match the target was also used to evaluate the online corrections that the participants made while trying to match the target. A lower coefficient of variation signified fewer corrections in the force production when attempting to match the target.

Separate repeated measures ANOVA (Age Group X pre/post-practice block) at a 0.05 alpha level were used to determine if there were differences in the behavioral performance of the participants between the pre- and post-practice blocks and by age group.

RESULTS

Motor Behavioral Results

Overall, our results showed that participants improved their ability to match the ankle forces that would accurately match the prescribed targets. For the number of targets matched, there was a significant main effect of pre-/post-practice block (Pre: 79 ± 3, Post: 87 ± 2; $P < 0.001$), which indicated that the participants improved the number of trials that they performed correctly. There was also a main effect of age group (Adolescent: 79 ± 3, Adults: 89 ± 2; $P = 0.02$), showing that the adults matched more targets. The interaction term was not significant ($P > 0.05$).

For the time to match the targets, there was a main effect of block (Pre: 2.33 ± 0.10 s, Post: 2.03 ± 0.09 s; $P < 0.001$), showing that the participants matched the targets faster after practice. There was also a main effect of age group (Adolescent: 2.40 ± 0.10

s, Adults: 1.97 ± 0.09 s; *P* = 0.017), showing that the adults matched the targets faster. The interaction term was not significant (*P* > 0.05).

For the target error, there was a main effect of pre-/post-practice block (Pre: 6.02 ± 0.73%, Post: 5.10 ± 0.68%; *P* = 0.036), showing that the participants had less errors in their force production after practice. There was no main effect of age group (Adolescent: 6.50 ± 0.62%, Adults: 4.66 ± 0.76%; *P* = 0.18). The interaction term was also not significant (*P* > 0.05).

For velocity, there was a main effect of pre-/post-practice block (Pre: 48.29 ± 3.54 N/s, Post: 61.46 ± 5.89 N/s; *P* = 0.002) as the participants had a faster velocity of the force production towards the target after practice. There was also a main effect of age group (Adolescent: 45.38 ± 3.64 N/s, Adults: 63.94 ± 5.57 N/s; *P* = 0.038), as the adults had a faster velocity of the force production towards the targets. The interaction term was not significant (*P* > 0.05).

For the reaction time, there was a main effect of pre-/post-practice (Pre: 0.448 ± 0.020 s, Post: 0.410 ± 0.014 s; *P* < 0.001), as the participants had faster reaction times after practice. There was also a significant main effect of age group (Adolescent: 0.487 ± 0.021 s, Adults: 0.375 ± 0.008 s; *P* < 0.001), as the adults responded faster than the adolescents. The interaction term was not significant (*P*s > 0.05).

Sensor-Level Results

When collapsing the data across the respective age groups and blocks (pre- and post-practice), there were significant alpha (8-14 Hz) and beta (18-32 Hz) ERDs that were present in a large number of sensors near the fronto-parietal region (*P* < 0.0001, corrected). These responses in the alpha band started near movement onset (0.0 s) and were sustained for approximately 0.6 s afterward (Figure 11). The responses in the beta

band started about 0.3 s before movement onset and were sustained for approximately 0.6 s afterward (Figure 11). For illustrative purposes, we show the pre- and post-practice time-frequency plots for each age group in Figure 11, but note that sensor-based statistics

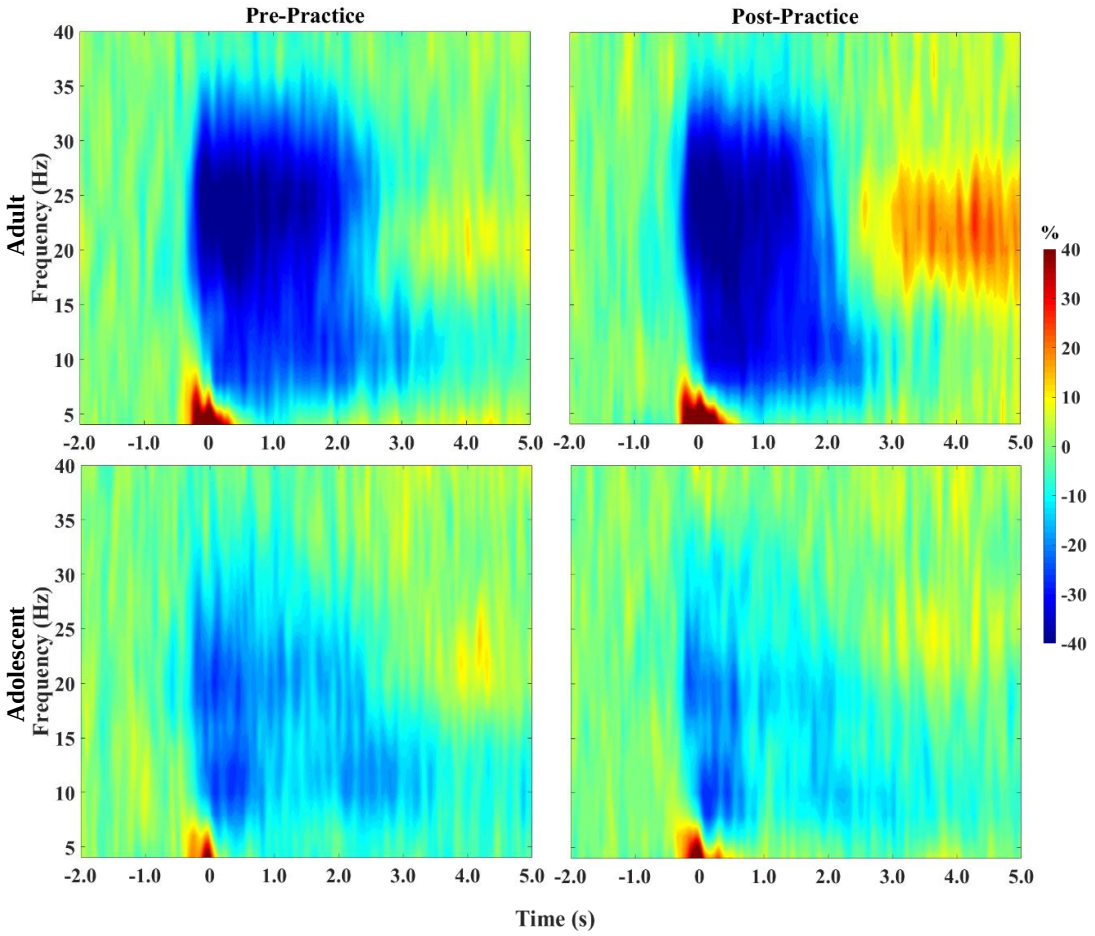

Figure 11: Group-averaged time-frequency spectrograms for pre- and post-practice blocks for the adolescent and adult groups. Frequency (Hz) is shown on the y-axis and time (s) is denoted on the x-axis, with 0 s defined as movement onset. The event-related spectral changes during the ankle plantarflexion target-matching task are expressed as percent difference from baseline (−2.0 to -1.4 s). The MEG gradiometer with the greatest response amplitude was located near the medial primary sensorimotor cortices, contralateral to the ankle used during the task. There was a strong desynchronization in the alpha (8 – 14 Hz) and beta (18 – 32 Hz) bands in both the pre- and post-practice blocks. As can be discerned, the strength of the alpha and beta desynchronization became notably weaker in the post-practice MEG session in the adolescents, but stronger in the adults. The color scale bar for all plots is shown to the far right.

were computed by collapsing the data across the practice blocks and age groups. Qualitative inspection of these figures shows that the strength of the alpha and beta ERDs appeared to become weaker after practice in adolescents but strengthen in adults.

Alpha Oscillations

The alpha (8-14 Hz) ERD identified in the sensor-level analysis within the 0.0 to 0.6 s time window was imaged using a beamformer. This analysis combined the MEG data acquired across the respective pre-/post-practice blocks and used a baseline period of -2.0 to -1.4 s. The resulting images were grand-averaged across pre-/post-practice blocks and age groups and revealed that the alpha ERD response was generated by parietal and occipital cortices (Figure 12). The local maximums seen in these cortical areas were subsequently used as seeds for extracting virtual sensor time courses (i.e., voxel time courses) from the pre and post-practice block images per participant. Peaks were found in the parietal and occipital cortices. Separate 2 X 2 mixed-model ANOVAs (pre/post-practice X adolescent/adult) were conducted on each peak to determine if the average virtual sensor activity during the motor execution stage (0 to 0.6 s) differed after practice and/or group in the parietal and occipital cortices.

For the parietal cortex, there was no significant main effect of pre-/post-practice in the alpha ERD response indicating that it was not affected by practice (P = 0.43, Figure 12A). There was a significant main effect of age group, suggesting the adults had stronger alpha ERD in the parietal cortex (P = 0.001). The interaction term was not significant (P = 0.075).

The results for the occipital cortex were similar, as there were no differences in the alpha ERD after practice (P = 0.082, Figure 12B). There was a significant main effect of age group, suggesting the adults had stronger alpha ERD in the occipital cortices (P = 0.003). The interaction term was not significant (P = 0.487). Hence, the alpha ERD in the parietal and occipital cortices was not affected by practice, but did differ with age.

Beta Oscillations

The beta (18-32 Hz) ERD identified in the sensor-level analysis between -0.3 and 0.3 s was imaged using a beamformer. Once again, this analysis combined the data acquired across the respective pre-/post-practice blocks and used a baseline period of −2.0 to -1.4 s. The resulting images were grand-averaged across pre-/post-practice blocks and age groups and indicated that the beta ERD was more centered on the leg region of the sensorimotor cortices (Figure 13), with additional bilateral clusters seen in the occipital cortices (Figure 14). As with the alpha analysis, the local maximums of these responses were next used as seeds for extracting virtual sensors from the pre and post-practice data blocks separately (per participant), and the virtual time courses from the two occipital peaks were averaged to create a single time series. Since the beta response

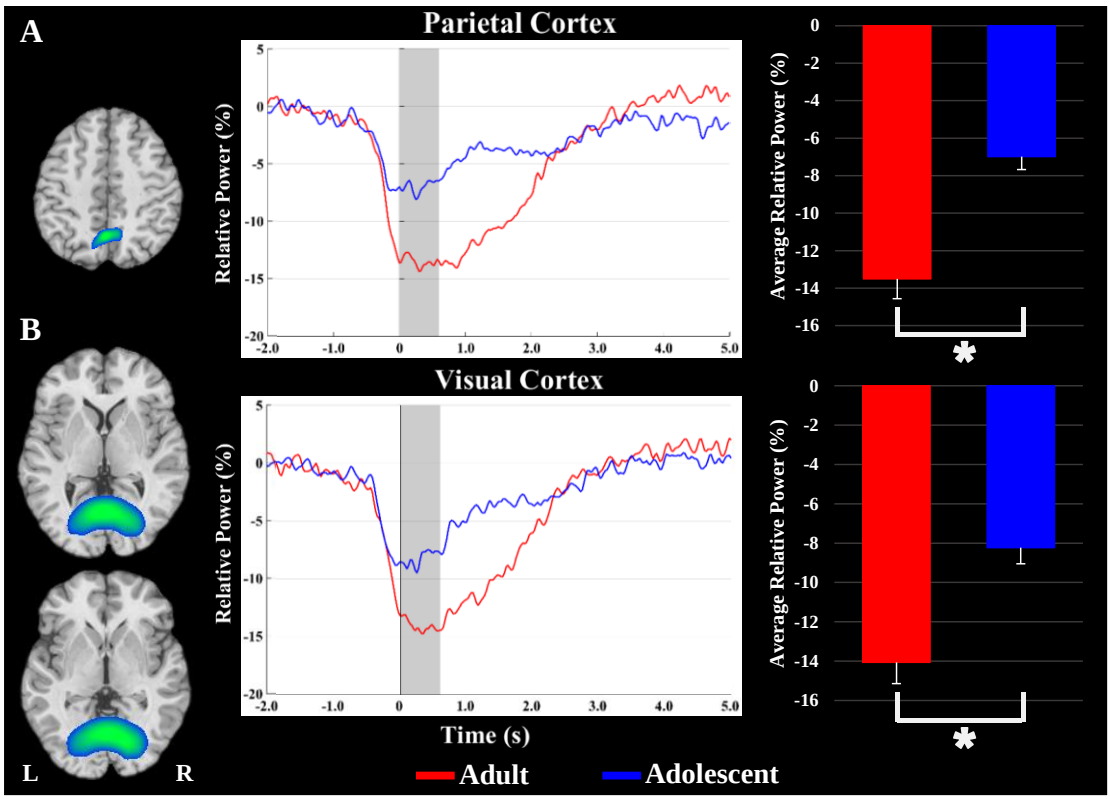

Figure 12: Grand averaged beamformer images and time series of alpha activity in the parietal and occipital cortices. Grand averaged beamformer images of alpha activity (8-14 Hz) from -0.0 to 0.6 s revealed two main clusters in the parietal (A) and occipital cortices (B). Time series data were extracted from the peak voxel in these clusters and are plotted with power changes relative to the baseline shown in a percent scale on the y-axis and time on the x-axis in seconds. There were age-related differences in the alpha event-related desynchronization (ERD) during motor execution (0 – 0.6 s) in both the parietal and occipital cortices. The time window that was used in the beamformer analysis and subjected to statistical analyses is denoted by the gray shading. There were no pre/post-practice differences in the alpha ERD during motor execution (0 – 0.6 s) in the parietal and occipital cortices. The bar graphs represent the average relative power during motor execution separated by age group (0 – 0.6 s).

extended across movement onset (i.e., 0.0 s), we conducted separate 2 x 2 x 2 mixed-model ANOVAs (pre/post-practice block X age group X time window) to determine if the average neural activity during the motor planning (-0.3 to 0 s) and execution stages (0 to 0.3 s) changed after practice in the sensorimotor and occipital cortices.

For the sensorimotor cortices, there was a main effect of time window (P = 0.001), which indicated that the strength of the beta ERD was stronger during the motor execution stage. There was also a main effect of age group (P < 0.001), which revealed that the adults had a stronger beta ERD compared to the adolescents across the motor planning

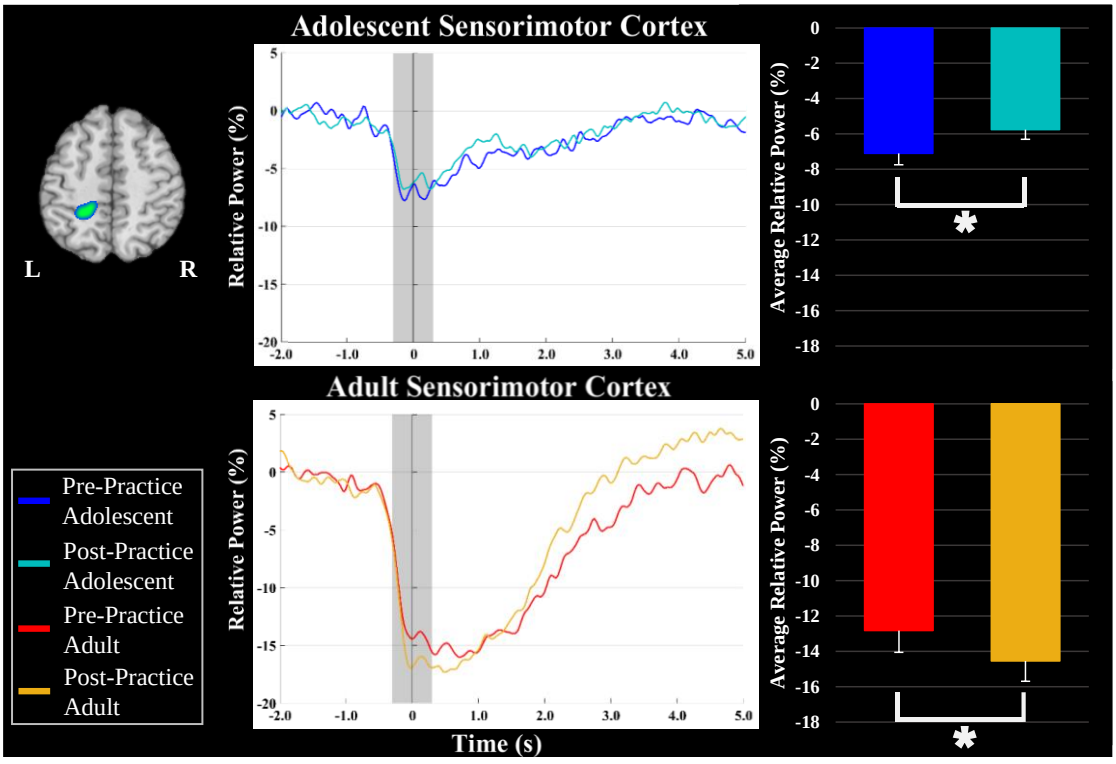

Figure 13: Grand averaged beamformer images and time series split by age group of beta activity in the sensorimotor cortices. Grand averaged beamformer images of beta activity (18-32 Hz) from -0.3 to 0.3 s revealed a main cluster in the sensorimotor cortices. Time series data were extracted from the peak voxel in this cluster, and are plotted as in Figure 12. The beta event-related desynchronization (ERD) response was stronger in adults relative to adolescents across the motor planning and execution (-0.3 – 0.3s) stages. There was also a significant interaction of age group by pre-/post-practice block. Post-hoc analysis showed that adolescents had a significantly weaker beta ERD and adults had significantly stronger ERD in the left sensorimotor cortices after practice. The bar graphs represent the average relative power across the motor planning and execution phases (gray areas) separated by age group and pre-/post-practice block (-0.3 – 0.3 s). Note that we did not examine the post-movement beta responses because we had no hypotheses about these, and because there were significant behavioral differences between pre- and post-practice, which would have biased any analyses.

and execution stages. There was no main effect of pre/post practice main effect ($P = 0.70$). However, there was a significant interaction between age group and pre/post practice ($P = 0.003$). Follow-up post hoc analyses showed that independent of the planning/execution time windows, the beta ERD was significantly stronger in the sensorimotor cortices of the adults after practice ($P = 0.004$, Figure 13), while the beta ERD was significantly weaker in the adolescents after practice. ($P = 0.01$, Figure 13).

For the occipital cortices, there was a significant main effect of time window ($P < 0.001$), indicating the power of the beta ERD in the occipital cortices was weaker during motor planning compared to the motor execution stage. There was no pre/post-practice ($P = 0.30$) or age ($P = 0.14$) main effect. However, the time window by age interaction term was significant ($P = 0.01$), and follow-up post hoc analyses showed that the beta ERD was significantly stronger in the occipital cortices during the motor execution stage for the adults ($P = 0.006$, Figure 14).

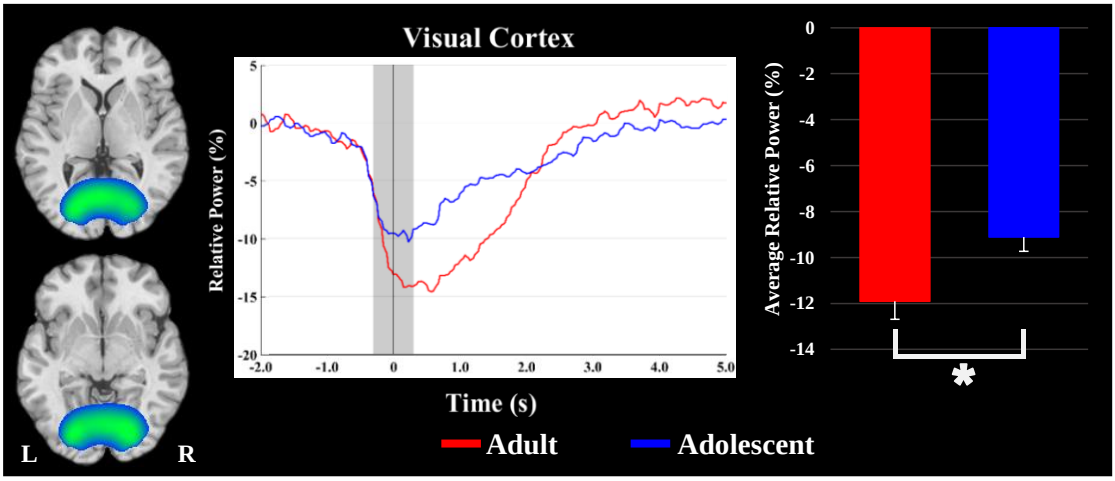

Figure 14: Grand averaged beamformer images and time series of beta activity in the occipital cortices. Grand averaged beamformer images of beta activity (18-32 Hz) from -0.3 to 0.3 s revealed a main cluster in the occipital cortices. Time series data were extracted from the peak voxel in these clusters, and are plotted as in Figure 12. Bilateral peaks were found in the occipital cortex and were averaged to create a single time series. There were significant group effects, whereby older adults exhibited a stronger beta event-related desynchronization (ERD) in the occipital cortex (gray shading). There were no pre-/post practice differences. The bar graphs represent the average relative power across the motor planning and execution stages separated by age group (-0.3 – 0.3 s).

DISCUSSION

There currently is a substantial knowledge gap in our understanding of how motor-related cortical oscillations are altered by practicing a novel motor task. Furthermore, we have limited insight on whether such practice effects are age-dependent. We used high-density MEG and advanced beamforming methods to begin to fill this knowledge gap by quantifying changes in the cortical oscillations of adults and adolescents after a short-term practice (e.g., fast-motor learning) session of a goal-directed, isometric, target-matching ankle plantarflexion task. The data-driven approach employed in this investigation revealed that there were notable differences between the adults and adolescents in the strength of the alpha and beta oscillatory activity in the sensorimotor, parietal and occipital cortical areas while generating the ankle plantarflexion force. However, only the beta cortical oscillations in the sensorimotor cortices changed after practice and were different between the two groups. These results imply that such beta oscillatory changes are likely central to the noted differences in the behavioral performance of the adults and adolescence after practice. Further discussion of the implications of our experimental results are discussed in the following sections.

One of our key findings was that the strength of the beta ERD in the leg region of the sensorimotor cortices changed differently in adolescents and adults after practicing the motor task. Specifically, the strength of the beta ERD in the adolescents became weaker after practice, while the strength of the beta ERD became stronger in adults. The reduced strength of the beta oscillations seen in the adolescents concurs with the numerous neuroimaging studies (e.g., fMRI, EEG, and PET) that have shown that the sensorimotor cortical activity is reduced after practicing a novel motor task (Galea & Celnik, 2009; Galea et al., 2011; Hadipour-Niktarash et al., 2007; Hatfield et al., 2004; Haufler et al., 2000; Hillman et al., 2000; Kranczioch et al., 2008; Orban de Xivry et al.,

2011; Reis et al., 2009; Zhang et al., 2011). This reduced cortical activity after practice may indicate that less cognitive and/or neural resources are required to successfully perform the motor task (Gehringer et al., 2018; Kelly & Garavan, 2005; Petersen et al., 1998; Poldrack, 2000). However, it has also been shown that task familiarity can differentially modulate the magnitude of sensorimotor cortical activity after practice (Hund-Georgiadis & von Cramon, 1999; Perez et al., 2004). Several investigations have shown that participants with minimal familiarity with the task exhibit a reduction in sensorimotor cortical activity after practice, while participants with prior experience with the motor task have an increase in their cortical activity (Hund-Georgiadis & von Cramon, 1999; Perez et al., 2004). These differential responses have been suggested to be related to the various stages of learning. Motor learning occurs in three distinct stages: 1) fast motor learning stage where there are rapid improvements in the task performance after a single practice session, 2) slow motor learning where there are incremental improvements across multiple practice sessions, and 3) offline learning where the motor memories are consolidated and skill stabilization occurs (Dayan & Cohen, 2011; Doyon & Benali, 2005; Fischer et al., 2005; Robertson et al., 2004). The decreased activity is presumed to represent the cortical changes that are associated with the fast motor learning stage where there are rapid improvements in the task performance after a single practice session, while the stronger activity is presumed to represent the cortical changes associated with the slow motor learning stage where there are incremental improvements across multiple practice sessions. We suggest that the different changes seen in the cortical activity between our groups after practice was related with prior familiarity with the motor task. For example, the adults were likely more skilled at performing the fine-motor ankle plantarflexions with their dominant right ankle due to their experience driving automobiles (i.e., pressing the gas pedal).

Our analysis also indicated that the strength of the beta ERD was stronger when adults both planned and execute a motor action relative to the adolescents. These results are well aligned with the prior literature (Gaetz et al., 2010a; Heinrichs-Graham et al., 2018). We suspect that the differences in the strength of the cortical oscillations may be partly related to maturational changes in brain structure, as it has been noted that the thickness of the sensorimotor cortices continues to thin and become refined well into late adolescence (Vandekar et al., 2015). Alternatively, the increased strength of the beta ERD with age could also be attributed to increased γ-aminobutyric acid (GABA) transmission (Gaetz et al., 2011; Heinrichs-Graham et al., 2018; Heinrichs-Graham & Wilson, 2016; Rossiter et al., 2014). The GABA system is still developing through adolescence (Kilb, 2012), and higher GABA levels have been linked to elevated motor-related oscillatory activity (Gaetz et al., 2011; Hall et al., 2011; Muthukumaraswamy et al., 2013), suggesting that adolescents should have lower levels of motor-related oscillatory activity.

Compared with the adults, our results also showed that the adolescents had weaker beta oscillations in the occipital cortices during the execution stage of the motor task. Prior experimental work has suggested that visual processing within occipital cortices can modulate the strength of activity within the cortical motor network during performance of a visuomotor task (Ledberg et al., 2007; Strigaro et al., 2015). Therefore, it is possible that the reduced beta oscillations seen in occipital cortices might indicate that the neural computations underlying visuomotor transformations during performance were suboptimal for the adolescents. Prior structural imaging has also shown that the behavioral performance of adolescents during a visuomotor task is influenced by the maturation of the optic radiations and the fronto-occipital fasciculus white matter tracts (Scantlebury et al., 2014). Hence, it is possible that the weaker beta oscillations seen in the occipital cortices may be related to maturation of these white matter fiber tracts.

The alpha ERD in parietal and occipital cortices was also weaker in the adolescents. The location and timing of these neural oscillations were in agreement with the breadth of literature suggesting that activity within these cortical areas supports the visuomotor transformations that are necessary for producing and correcting a motor action (Beurze et al., 2007; Buneo & Andersen, 2006; Della-Maggiore et al., 2004; 2013; Gallivan et al., 2011; Kurz et al., 2016; Valyear & Frey, 2015). The weaker alpha oscillations seen in these cortical areas may imply that adolescents have more difficulty computing these transformations. Nevertheless, the results of the current experiment imply that motor-related alpha oscillations do not appreciably change after short-term practice in adolescents or adults. This is somewhat perplexing since prior MEG and EEG studies have noted that alpha oscillations in sensors/electrodes near the sensorimotor cortices become weaker after practicing a motor sequence with the fingers (Leocani et al., 1997; Pollok et al., 2014). We speculate that these discrepancies might reside in the differences between implicit and explicit learning. The finger motor action sequence learned in these previous studies was acquired implicitly, while the ankle motor action learned in this investigation was acquired explicitly.

In conjunction with the noted changes in the sensorimotor beta oscillatory activity, both the adults and adolescents had significant improvements in their motor performance for all of the outcome measurements. However, the adults performed the motor task better as they matched more targets, and matched the targets faster after practice. Prior behavioral work has shown that adolescents require more practice in order to reach motor performance levels that are similar to adults (Goh et al., 2012; Sullivan et al., 2008). Our results appear to follow this notion since the adolescents did not achieve the same performance levels as the adults after practicing the same number of trials. Potentially the differences in the extent of changes seen in the adolescents after practice may simply

arise from inexperience and the need for more trials to achieve similar outcomes as the adults (Contreras-Vidal, 2006; 2005; Goble et al., 2005; King et al., 2009; 2012; Pangelinan et al., 2013; 2011).

Overall, the results from this investigation showed that the strength of the alpha and beta oscillations seen in the parietal, occipital and sensorimotor cortices during leg motor actions are different in adults and adolescents, and that the strength of beta sensorimotor cortical oscillations change differently after adolescents and adults practice a motor task. We suspect that these noted differences might be related to familiarity with the motor task, GABA levels, and/or maturational differences in the integrity of the white matter fiber tracts that connect the involved cortical areas.

CHAPTER 3: THE STRENGTH OF THE MOVEMENT-RELATED SOMATOSENSORY CORTICAL OSCILLATIONS DIFFER BETWEEN ADOLESCENTS AND ADULTS

INTRODUCTION

Adolescents demonstrate greater mastery of single joint movements, drawing, aiming, reaching and grasping objects as they become older (Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Fayt et al., 1992; Hay et al., 1991; Jansen-Osmann et al., 2002; Kuhtz-Buschbeck et al., 1998; Yan et al., 2000). Although this is a common finding, there is no consensus on why motor control improves during this developmental stage. One of the prevailing hypothesis is that maturation of the somatosensory system during adolescence might contribute to the improved motor control (Cignetti et al., 2013; 2017; Goble et al., 2005; King et al., 2009; 2012). Essentially, adolescents may have a diminished ability to detect errors in their selected motor actions because their interpretation of the sensory feedback is less precise and delayed (Angel & Malenka, 1982; Gori et al., 2012; Holst-Wolf et al., 2016; King et al., 2009; 2012; Milne et al., 1988). Alternatively, other investigations have hypothesized that the motor control differences may not be related to the quality of the sensory feedback, but rather adolescents are less experienced at properly weighting all of the available sensory feedback during a movement (*i.e.,* muscle spindle, joint position, visual tracking) (Cignetti et al., 2013; 2017; Goble et al., 2005). While both of these alternative hypotheses are plausible, limited efforts have been made to determine if there is a connection between the somatosensory cortical processing and the motor actions seen in adolescents.

Predominantly, our understanding of movement-related somatosensory attenuation (i.e., gating) has been derived from event related potential (ERP) studies of peripheral nerve stimulation (Jones et al., 1989; Kristeva-Feige et al., 1996; Macerollo et al., 2016; Papakostopoulos et al., 1975). Overall these studies have shown that the

amplitude of the evoked somatosensory cortical activity is attenuated during movement. Although these outcomes have been pivotal for advancing our understanding of sensorimotor integration and motor-related gating, the neural oscillatory activity is certain to play a computational role in such processing, and this domain remains for the most part completely unexplored. Focusing on the neural oscillations may provide unique and important insight about the cortical dynamics that are not directly phase-locked to the peripheral stimulus. It is well recognized that peripheral stimulation of the foot while sitting quietly produces an immediate and transient synchronization (e.g., increase in power) of the somatosensory cortical oscillations across the 10-75 Hz frequency bands (Kurz et al., 2014b; 2015; 2017b; Wiesman et al., 2017). These neural synchronizations are followed by a desynchronization (e.g., decrease in power) across the alpha (8-16 Hz) and beta (18-26 Hz) and frequency bands during the later time window (150 ms-400ms). It has also been shown that the neural synchronizations seen across the theta-beta frequency range (6-24 Hz) are sustained while performing a haptic task, while the other frequency bands that were seen in the no movement condition are completely gated (Kurz et al., 2018). Although our knowledgebase on how changes in the strength of the somatosensory cortical oscillations reflect the differences in sensory processing is rapidly expanding, whether these cortical oscillations are different between adolescents and adults during movement remains unknown.

In the present study, we used magnetoencephalographic (MEG) brain imaging to begin addressing this knowledge gap by applying an electrical stimulation to the tibial nerve as adolescents and adults generated an isometric ankle plantarflexion force, or sat quietly with no motor activity (e.g., passive condition). Our key hypotheses were: 1) that for both groups the strength of the somatosensory cortical oscillations would be altered while producing the isometric force relative to the passive condition, and 2) that the magnitude the attenuation of the somatosensory cortical oscillations while producing the

isometric force would be significantly different between the adolescents and adults.

MATERIAL AND METHODS

Subjects

Nineteen adolescents (Age = 14.8 ± 2.5 yrs.; Female = 9; Right handed = 19) and nineteen adults (Age = 36.8 ± 5.0; Female = 9; Right handed = 19) with no neurological or musculoskeletal impairments were recruited to participate in this study. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation, and all participants or their guardians provided informed consent or assent prior to participation in the study.

MEG Data Acquisition and Experimental Paradigm

All MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. Neuromagnetic responses were acquired with a bandwidth of 0.1 – 330 Hz and were sampled continuously at 1 kHz using an Elekta Neuromag system (Helsinki, Finland) with 306 MEG sensors, including 204 planar gradiometers and 102 magnetometers. With the use of the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006).

The participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. Unilateral electrical stimulation was applied to the right posterior tibial nerve using external cutaneous stimulators that were connected to a Digitimer DS7A constant-current stimulator system (HW Medical Products, Neuberg, Germany). During stimulation, each participant sat quietly focused on a fixation cross (passive condition), or performed an ankle isometric force target matching

task (active condition). During both the passive and active conditions, single 0.2 ms constant current square waves were presented using an interstimulus interval that randomly varied between 1800 and 2200 ms. The amplitude of the pulses was set to the threshold required to elicit a visible flexor twitch in the hallux and was constant for both conditions.

During the active condition, the participants were instructed to generate an isometric ankle plantarflexion force with the right leg. A custom-built magnetically-silent pneumatic force transducer was used to measure the isometric forces was concurrently sampled at 1 kHz along with the MEG data (Figure 15) (Arpin et al., 2018; Gehringer et al., 2018). The experimental task consisted of the participant generating an isometric force that would animate a box to ascend vertically and shoot through a target box. The target boxes had vertical positions that were between 5-30% of the participant's maximum isometric ankle plantarflexion force and their positions were randomly determined. The respective boxes were visually displayed on a back-projection screen that was ~1 meter in front of the participant at eye level. Each participant generated ~200 isometric plantarflexion forces. Each trial lasted 1500 ms and was followed by an 800 ms rest period. Only those trials where electrical stimulation occurred during the isometric force were selected for analysis.

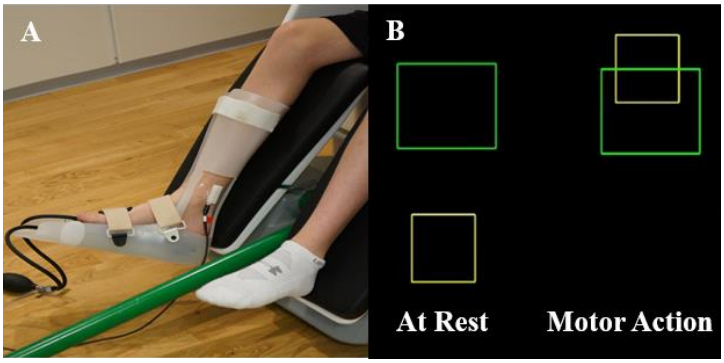

Figure 15: Participant seated in the MEG chair with the electrical stimulator placed over the tibial nerve and exemplary visual feedback. A) Participant seated in the MEG chair with the electrical stimulator placed over the tibial nerve and the custom pneumatic ankle force system on their right leg. B) Exemplary visual feedback displayed to the participant. The isometric ankle plantarflexion forces generated by the participant animated the vertical position of a yellow box's position on the screen. The goal of the task was to generate an isometric force that shot the yellow box through the presented green target box.

MEG Coregistration

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (*e.g.*, 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed for each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered with native space neuroanatomical MRI data using three external landmarks (*i.e.*, fiducials), and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

MEG Pre-Processing, Time-Frequency Transformation, & Statistics

Using the MaxFilter software (Elekta), each MEG data set was individually corrected for head motion that may have occurred during the task performance, and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. The number of trials were balanced between age group and condition, and were tested using a mixed model ANOVA (Adolescent/Adult Group X Active/Passive Condition), showing no significant difference between the number of trials per age group or condition ($Ps > 0.05$). The continuous

magnetic time series was divided into epochs of 1100 ms in duration (-500 to 600 ms), with the onset of the electrical simulation defined as 0 ms and the baseline defined as -200 to 0 ms. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation and averaged over the respective trials. These sensor-level data were normalized by dividing the power value of each time-frequency bin by the respective bin's baseline power, which was calculated as the mean power during the baseline (−200 to 0 ms). The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Briefly, each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point and the output spectrogram of t-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants and conditions. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the ($p < 0.05$) threshold, and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris & Oostenveld, 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

MEG Source Imaging

A minimum variance vector beamforming algorithm was employed to calculate the source power across the entire brain volume using a spherical head model (Gross et al.,

2001). The single images were derived from the cross spectral densities of all combinations of MEG sensors and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Hillebrand & Barnes, 2005; Hillebrand et al., 2005; Van Veen et al., 1997). Thus, the normalized power per voxel was computed over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. Each participant's functional images, which were co-registered to anatomical images prior to beamforming, were transformed into standardized space using the transform previously applied to the structural MRI volume and spatially resampled. MEG pre-processing and imaging used the Brain Electrical Source Analysis (BESA) software (BESA v6.0; Grafelfing, Germany).

Time series analysis was subsequently performed on the neural activity extracted from the peak voxel in the grand-averaged beamformer images (see Results below). The virtual neural time courses were created by applying the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which resulted in a time series with the same temporal resolution as the original MEG recording (Cheyne et al., 2006; Heinrichs-Graham et al., 2016; Heinrichs-Graham & Wilson, 2016). Once the neural time courses were extracted, they were transformed into the time-frequency domain, and the two orientations for each peak voxel per individual were combined using a vector-summing algorithm. The power of these time courses, relative to baseline, was averaged across the window of interest for each individual to assess the key oscillatory responses. The data was then collapsed across groups and paired-samples t-tests were used to test if condition had an effect on the power of the somatosensory responses. Further, to test if the attenuation of the somatosensory response was different between groups, the average difference of the power (Passive – Active) during time-frequency windows was tested using a two-sample t-test.

RESULTS

Sensor-Level Results

When collapsing the data across the respective conditions (active and passive) and age groups, a series of significant oscillations were detected in a cluster of gradiometers near the fronto-parietal region. The sensor-level spectrograms revealed significant alpha-beta (8-30 Hz) and gamma (38-80 Hz) event related synchronizations (ERS) that were initiated immediately after the stimulation and were sustained for 125ms and 100ms, respectively ($P < 0.0001$, corrected). In addition, a significant beta (18-26 Hz) event related desynchronization (ERD) was observed during the latter 300-400 ms time window ($P < 0.0001$, corrected).

Gamma Oscillations

The beamforming of the gamma (38-80 Hz) ERS was performed within the 0 to 100 ms time window by combining the MEG data acquired across the respective conditions and age groups and used a baseline period of −125 to -25 ms. These images revealed that the gamma ERS response was generated by the leg region of the contralateral somatosensory cortex (Figure 16A). The local maximum seen in this cortical area was subsequently used to extract virtual neural time courses from the active and

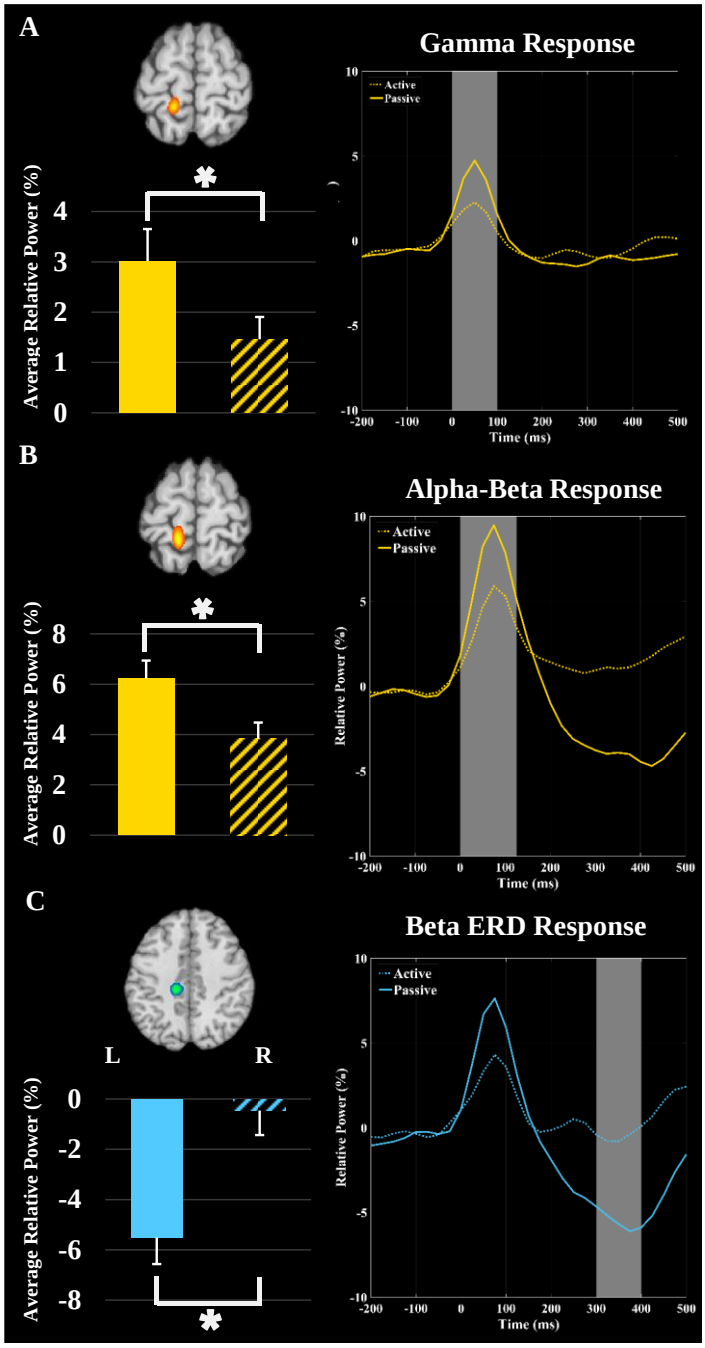

Figure 16: Grand averaged beamformer images for the oscillatory activity in the somatosensory cortex, the neural time course, and the average relative power for the active and passive conditions. Grand averaged beamformer images for the active and possive conditions for (A) gamma activity (38-80 Hz) from 0 to 100 ms, (B) alpha-beta activity (8-30 Hz) from 0 to 125 ms, and (C) beta oscillations (18-26 Hz) from 300 to 400 ms revealed main clusters in the somatosensory cortex. The neural time course displayed were extracted from the peak voxel in respective beamformer images. The solid line reprsents the neural time course during the passive condition, while the dash line repesents the acive condition. The bar graphs represent the average relative power from 0 to 100 ms for gamma activity (38-80 Hz), 0 to 125 ms for alpha-beta activity (8-30 Hz), and 300 to 400 ms for beta oscillations (18-26 Hz). Significant power differences are denoted by the asterisk ($P \leq 0.05$). As shown, the strength of the somatosensory cortical activity was significantly weaker (e.g., gated) while the participants generated the isometric ankle plantarflexion force.

passive images for each participant and the average activity across the 0 to 100 ms time window was subsequently calculated. There was a significant difference in the power of the somatosensory response between conditions, indicating that the strength of the gamma ERS was weaker during the active condition (P = 0.014, Figure 16A). However, there was no difference in the amount of attenuation between the groups (P = 0.67). Hence, indicating that the attenuation of the gamma ERS overall was similar between the adolescents and adults.

Alpha-Beta Event-Related Synchronization

The beamforming of the alpha-beta (8-30 Hz) ERS within the 0 to 125 ms time window was also performed by combining the data acquired across conditions and age

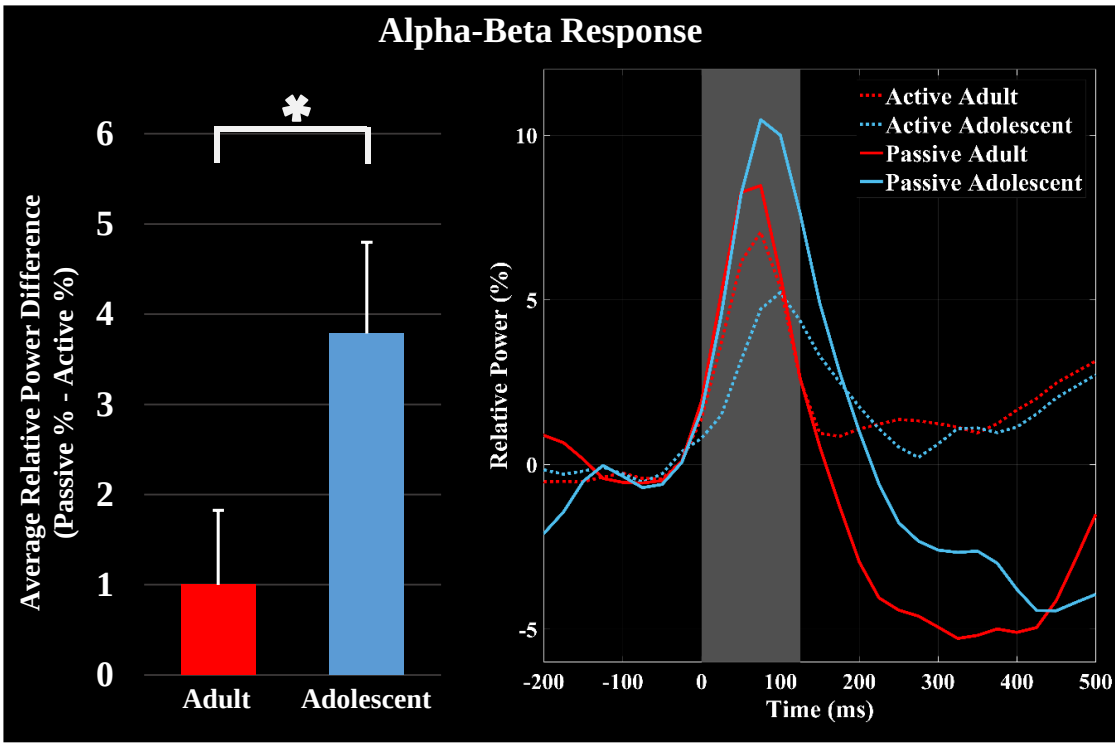

Figure 17: Average of the neural time courses the amount of attenuation of the average relative power of alpha-beta ERS split by age group. Average of the neural time courses extracted from the peak voxel in the alpha-beta grand averaged beamformer images for the adolescents (blue) and adults (red). The solid line represents the neural time course for the passive condition, while the dashed line represents the neural time course for the active condition. The bar graphs show the amount of attenuation (Passive – Active) of the average relative power of alpha-beta event related synchronization (ERS) during the 0 – 125 ms time window. Significant differences in the magnitude of attenuation are denoted by the asterisk ($P \leq 0.05$). As shown, the adolescents had greater attenuation (e.g., gating) of the alpha-beta ERS during the isometric ankle plantarflexion task.

groups, and used a baseline period of −150 to -25 ms. The alpha-beta ERS was also centered in the leg region of the contralateral somatosensory cortex (Figure 16B). The local maximums seen in this cortical area were subsequently used to extract the virtual time courses from the active and passive condition images for each participant, and the average activity across the 0 to 125 ms time window was subsequently calculated. There was a significant difference in the power of the somatosensory response between conditions (P = 0.016, Figure 16B), which revealed that the alpha-beta ERS was significantly weaker during the active condition. Additionally, the attenuation between the groups was significantly different (P = 0.045, Figure 17), indicating that the attenuation of the alpha-beta ERS was greater in the adolescents.

Beta Event-Related Desynchronization

The beamforming of the beta (18-26 Hz) ERD that was noted in the time-frequency spectrograms within the 300 to 400 ms time window was performed by combining the data acquired across conditions and age groups and used a baseline period of −125 to -25 ms. The beta ERD was also centered on the leg region of the contralateral somatosensory cortex (Figure 16C). The local maximums seen in this cortical area were subsequently used to extract the virtual neural time courses from the active and passive condition images per participant and the average activity across the 300 to 400 ms time window was subsequently calculated. There was a significant difference in the power of the somatosensory response between conditions ($P < 0.001$, Figure 16C), revealing that the

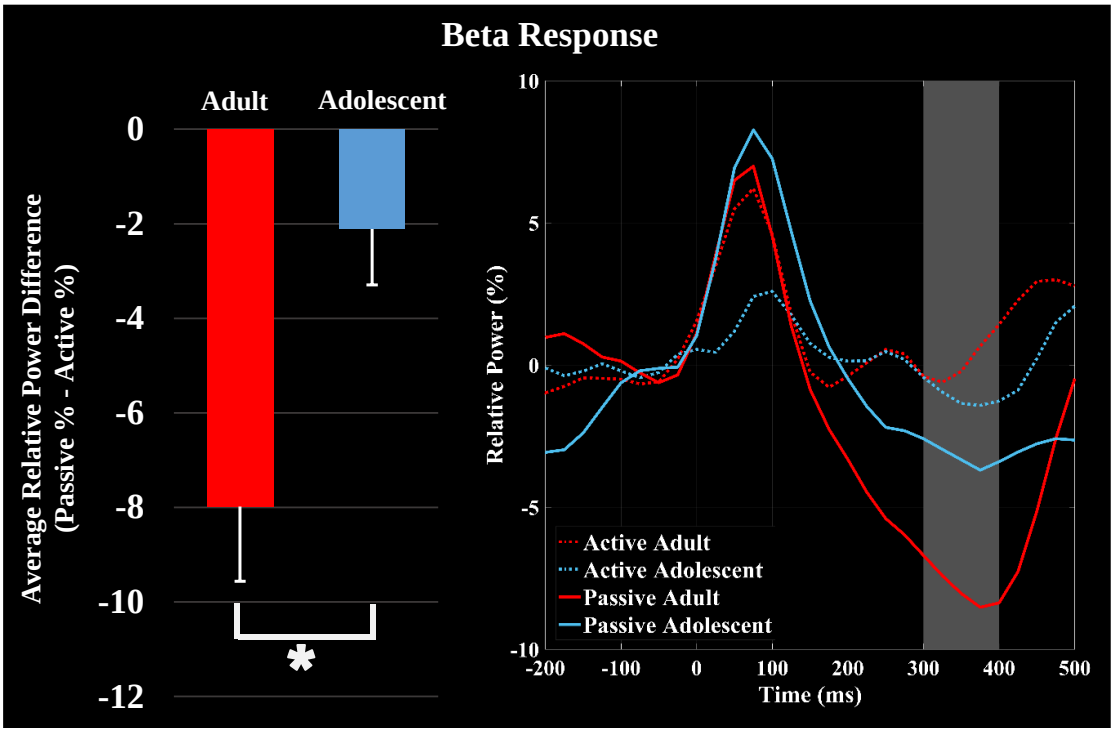

Figure 18: Average of the neural time courses the amount of attenuation of the average relative power of beta ERD split by age group. Average of the neural time courses extracted from the peak voxel in the beta grand averaged beamformer images for the adolescents (blue) and adults (red). The solid line represents the neural time course for the passive condition, while the dashed line represents the neural time course for the active condition. The bar graphs show the amount of attenuation (Passive – Active) of the average relative power of beta event related desynchronization (ERD) during the 300 – 400 ms time window. Significant differences in the magnitude of attenuation are denoted by the asterisk (P<0.05). As shown, the adults had greater attenuation (e.g., gating) of the beta ERD during the isometric ankle plantarflexion task.

beta ERD was significantly weaker during the active condition. Additionally, the attenuation between the groups was significantly different (P = 0.029, Figure 18), indicating that the attenuation of the beta ERD was greater in the adults.

DISCUSSION

This investigation used MEG and advanced beamforming to quantify changes in the somatosensory cortical oscillations while sitting quietly (e.g., passive condition) and while producing an ankle plantarflexion isometric force. The data-driven approach employed in this investigation revealed that for both conditions there were an alpha-beta (8-30 Hz, 0-125 ms) and a gamma (38-80 Hz, 0-100 ms) ERS in the leg region of the contralateral somatosensory cortices that occurred immediately after the peripheral stimulation. Subsequently, these oscillatory changes were followed by a beta ERD (18-26 Hz) that occurred in the later time window (300-400 ms). When compared with the passive condition, all of these frequency specific cortical oscillations were weaker while the participants produced the isometric force. However, the adolescents demonstrated greater attenuation of the alpha-beta ERS, while the adults had greater attenuation of the beta ERD. These results imply that altered attenuation of the respective cortical oscillations might be central to the uncharacteristic somatosensory processing previously reported in the behavioral literature for adolescents, and may partly underlie the altered motor performance characteristics seen in adolescents (Angel & Malenka, 1982; Gori et al., 2012; Holst-Wolf et al., 2016; King et al., 2009; 2012; Milne et al., 1988). Further interpretation of our experimental results are discussed in the proceeding sections.

The strength of the gamma ERS in the somatosensory cortex was significantly weaker during the active condition, but the amount of attenuation was not different between the adults and adolescents. This implies that this frequency specific somatosensory processing is mature by adolescents and likely does not underlie the

motor control differences previously reported for adolescents. The gamma cortical oscillations are typically associated with higher-order information processes, such as attention (Bauer et al., 2006; Gaetz et al., 2012; Ray et al., 2008). Prior MEG research has shown that the gamma ERS in the somatosensory cortex tends to be stronger when the participants attend to the peripheral stimulation (Dockstader et al., 2010). Based on this evidence, it is possible that the reduction in the gamma ERS seen during the motor task may be driven by allocation of attentional resources. In other words, the somatosensory gamma ERS was gated during the movement because more attentional resources were allocated towards generating the isometric muscular force.

Our results also showed that the strength of the alpha-beta ERS in the somatosensory cortex was also significantly weaker while the participants generated the isometric ankle plantarflexion force. This conditional effect is aligned with the prior results from EEG with humans and animal model studies (Houdayer et al., 2006; Jones et al., 1989; Kristeva-Feige et al., 1996; Macerollo et al., 2016; Papakostopoulos et al., 1975; Seki & Fetz, 2012; Seki et al., 2003). Additionally, our analysis identified that the adolescents exhibit a greater attenuation of the alpha-beta ERS while generating the isometric force. We suggest that the greater attenuation indicates that the adolescents have greater difficulty processing somatosensory feedback during volitional motor actions. Similar to the conjecture put forth in the preceding paragraph, we suspect that the excessive hyper-gating may be a result of allocation of resources that are necessary for simultaneously processing the sensory feedback and generating the isometric force.

In contrast with the alpha-beta ERS, the attenuation of the beta ERD in the somatosensory cortex in the later time period was greater for the adults. This response is often considered to be a rebound or resetting of the somatosensory cortical oscillations (Boto et al., 2017; Chien et al., 2014; Della Penna et al., 2004; Nikouline et al., 2000;

Svoboda et al., 2004). Hence, it is possible that the adolescents uncharacteristically reset the somatosensory cortical oscillations while generating the isometric force, while the adults tend to continue to process the ongoing somatosensations. Alternatively, it has been postulated that these later oscillations may be a result of the sensory information generated through the electrical stimulation of the peripheral alpha motor neurons and/or Ia afferents that interface with the muscle spindles (Kurz et al., 2018). This is based on the premise that excitation of the Ia afferents with a low-grade electrical stimulation augments the Hoffman reflex (Grosset et al., 2007; Tucker et al., 2005; Zehr, 2002). This reflexive pathway generates a muscular twitch via the monosynaptic connections between the Ia afferents and alpha motor neurons in the anterior horn of the spinal cord. A prior study that has established that the magnitude of the Hoffman reflex scales with age throughout adolescents (Grosset et al., 2007). Therefore, it is plausible that the altered beta ERD might be linked with the maturation of the Hoffman reflex.

CONCLUSIONS

Our results show that all of the frequency specific somatosensory cortical oscillations are reduced while producing an ankle plantarflexion isometric force. However, attenuation of the alpha-beta somatosensory ERS while producing an isometric force appears to be greater in adolescents when compared with adults. In contrast, adults have a greater attenuation of the beta ERD. These results imply that alterations frequency specific somatosensory cortical oscillations may partly underlie the altered motor performance characteristics reported in literature for adolescents.

DISCUSSION

The first main purpose of this dissertation was to identify how the sensorimotor cortical oscillation change after typically developing young adults practice a novel motor task with their non-dominant ankle. This dissertation specifically explored the alpha and beta band oscillatory activity that was generated by the sensorimotor and occipital cortices before and after practicing an isometric ankle plantarflexion target matching task with their non-dominant ankle. The main objective of the first investigation was to use high-density MEG to begin to address these knowledge gaps by quantifying how the alpha and beta cortical oscillations during the motor planning and execution stages are altered after a short-term practice session involving an ankle plantarflexion motor task. The outcomes from this main purpose would provide fundamental information on how fast motor learning alters the sensorimotor oscillatory activity.

Our results found that fast-motor learning results in a reduced amount of power in the beta ERD seen in the sensorimotor and visual cortices. These results concur with previous fMRI, EEG, and PET investigations that have shown that activation changes primarily reside in the sensorimotor network after practicing a novel motor task (Classen et al., 1998; Galea & Celnik, 2009; Galea et al., 2011; Hadipour-Niktarash et al., 2007; Hatfield et al., 2004; Haufler et al., 2000; Hillman et al., 2000; Kranczioch et al., 2008; Orban de Xivry et al., 2011; Reis et al., 2009; Zhang et al., 2011). These changes in the sensorimotor cortices likely reflect the reduction in neuronal resources needed to perform a motor action. The changes in the visual cortices during the planning phase may reflect a reduction of the weighting of visual information. Prior studies have implied that the occipital cortices contribute to the visuomotor transformations that are necessary for planning a motor action that will match the prescribed target location (Krigolson et al., 2015; Kurz et al., 2017a; Messier & Kalaska, 1997; Shadmehr & Mussa-Ivaldi, 1994). The

beta ERD changes were concurrent with improvements in task performance, which indicate these cortical changes reflect fast motor learning. Additionally, we found no changes in the alpha cortical oscillations. These results are somewhat perplexing since prior MEG and EEG studies have noted that alpha oscillations in sensors near the sensorimotor cortices became weaker after practicing a motor sequence with the fingers (Leocani et al., 1997; Pollok et al., 2014). We speculate that these discrepancies might reside in the differences between implicit and explicit learning. However, while this explanation is conceivable, it needs to be experimentally challenged before it can be fully supported.

The second main purpose of this dissertation sought to establish how the changes of the sensorimotor cortical oscillations differ between adolescents and adults when using their dominant ankle. This main purpose attempted to build upon the findings in Chapter 1. This dissertation specifically explored the alpha and beta band oscillatory activity that was generated by the sensorimotor and occipital cortices before and after practicing an isometric ankle plantarflexion target matching task with their dominant ankle in a cohort of both typically developing adolescents and adults. The main objective of the second investigation was to use high-density MEG to identify how practicing an ankle plantarflexion target matching task differentially affects motor-related alpha and beta oscillations in adults and adolescents. The outcomes from this main purpose would begin to address the clear gap in the scientific literature regarding the impact of practicing a motor task on cortical beta oscillations in adolescents, providing a greater understanding of why the adolescent brain is less efficient at executing motor plans and interpreting the somatosensory feedback.

The results from this investigation showed that the strength of the alpha and beta oscillations seen in the parietal, occipital and sensorimotor cortices during leg motor actions are different in adults and adolescents, and that the strength of beta sensorimotor

cortical oscillations change differently after adolescents and adults practice a motor task. Specifically, the strength of the beta ERD in the adolescents became weaker after practice, while the strength of the beta ERD became stronger in adults. The reduction in power in the adolescents mirrors what was seen in Chapter 1. However, it has also been shown that task familiarity can differentially modulate the magnitude of sensorimotor cortical activity after practice (Hund-Georgiadis & von Cramon, 1999; Perez et al., 2004). These differential responses have been suggested to be related to the various stages of learning. The decreased activity is presumed to represent the cortical changes that are associated with the fast motor learning stage where there are rapid improvements in the task performance after a single practice session, while the stronger activity is presumed to represent the cortical changes associated with the slow motor learning stage where there are incremental improvements across multiple practice sessions. We suggest that the different changes seen in the cortical activity between our age groups after practice was related with prior familiarity with the motor task. Incidentally, we suggest the increased strength of the beta ERD with age, independent of practice block, could also be attributed to increased γ-aminobutyric acid (GABA) transmission (Gaetz et al., 2011; Heinrichs-Graham et al., 2018; Heinrichs-Graham & Wilson, 2016; Rossiter et al., 2014). The GABA system is still developing through adolescence (Kilb, 2012), and higher GABA levels have been linked to elevated motor-related oscillatory activity (Gaetz et al., 2011; Hall et al., 2011; Muthukumaraswamy et al., 2013), suggesting that adolescents should have lower levels of motor-related oscillatory activity.

The third main purpose of this dissertation assessed how the movement-related attenuation of the somatosensory response differed between adolescents and adults. This investigation used MEG to quantify changes in the somatosensory response to an electrical stimulation applied to the tibial nerve while sitting quietly and while producing an

ankle plantarflexion isometric force. One of the prevailing hypotheses on why motor control improves during this developmental stage is that maturation of the somatosensory system during adolescence might contribute to the improved motor control (F. Cignetti, Chabeauti, Sveistrup, Vaugoyeau, & Assaiante, 2013; 2017; Goble, Lewis, Hurvitz, & Brown, 2005; King, Kagerer, Contreras-Vidal, & Clark, 2009; 2012). Essentially, adolescents may have a diminished ability to detect errors in their selected motor actions because their interpretation of the sensory feedback is less precise and delayed (Angel & Malenka, 1982; Gori et al., 2012; Holst-Wolf, Yeh, & Konczak, 2016; King et al., 2009; 2012; Milne, Aniss, Kay, & Gandevia, 1988). Alternatively, other investigations have hypothesized that adolescents are less experienced at properly weighting all of the available sensory feedback during a movement (F. Cignetti et al., 2013; 2017; Goble et al., 2005). The outcomes from this main purpose will increase our understanding of how the somatosensory system might contribute to motor learning differences seen in adolescence.

The results of this investigation revealed that for both conditions there were an alpha-beta and a gamma ERS in the leg region of the contralateral somatosensory cortices that occurred immediately after the peripheral stimulation. Subsequently, these oscillatory changes were followed by a beta ERD that occurred in the later time window. When compared with the passive condition, all of these frequency specific cortical oscillations were weaker while the participants produced the isometric force. The strength of the gamma ERS in the somatosensory cortex was significantly weaker during the active condition, but the amount of attenuation was not different between the adults and adolescents. It is possible that the reduction in the gamma ERS seen during the motor task may be driven by allocation of attentional resources, as prior MEG research has shown that the gamma ERS in the somatosensory cortex tends to be stronger when the

participants attend to the peripheral stimulation (Dockstader et al., 2010). Additionally, our analysis identified that the adolescents exhibit a greater attenuation of the alpha-beta ERS while generating the isometric force. We suggest that the greater attenuation indicates that the adolescents have greater difficulty processing somatosensory feedback during volitional motor actions. We suspect that the excessive hyper-gating may be a result of allocation of resources that are necessary for simultaneously processing the sensory feedback and generating the isometric force. In contrast with the alpha-beta ERS, the attenuation of the beta ERD in the somatosensory cortex in the later time period was greater for the adults. It has been postulated that these later oscillations may be a result of the sensory information generated through the electrical stimulation of the peripheral alpha motor neurons and/or Ia afferents that interface with the muscle spindles (Kurz et al., 2018). This is based on the premise that excitation of the Ia afferents with a low-grade electrical stimulation augments the Hoffman reflex (Grosset, Mora, Lambertz, & Perot, 2007; Tucker, Tuncer, & Turker, 2005; Zehr, 2002). This reflexive pathway generates a muscular twitch via the monosynaptic connections between the Ia afferents and alpha motor neurons in the anterior horn of the spinal cord. A prior study that has established that the magnitude of the Hoffman reflex scales with age throughout adolescents (Grosset et al., 2007). Therefore, it is plausible that the altered beta ERD might be linked with the maturation of the Hoffman reflex.

LIMITATIONS

The research in this dissertation were limited as the studies were cross sectional and not longitudinal. Although these results presented in Chapters 1 through 3 provide novel information about how the sensorimotor oscillatory activity differs between adolescents and adults, a follow up study would been needed to see how these changes develop across a lifetime. Additionally, we did not take any measure of amount of physical

activity levels of the participants in these investigations. Chapter 2 suggested that prior experience performing a motor task can modulate how the sensorimotor cortical oscillations change. The results may be more robust if we could include the participants' level of physical activity, or more specifically their level of experience performing similar tasks. Including these data in our statistical models may lead to a greater understanding of the variance in our results. Additionally, the results presented in Chapters 1 and 2 showed no relationship between the changes in the motor performance and the oscillatory activity. This may suggest that the changes in the visuomotor network may be a part of a change in the overall motor network. Motor learning involves interactions between the visuomotor networks, subcortical structures, like the basal ganglia and cerebellum, and the spinal cord (Doya, 2000; Doyon & Benali, 2005; Doyon & Ungerleider, 2002; Hikosaka et al., 2002; Seger, 2006; Vahdat et al., 2015). Changes that occur in the subcortical regions and spinal cord may be linked with the changes in motor performance but further investigation would be needed to fully determine this relationship.

FUTURE DIRECTIONS

The results of this work support the theory that differences in somatosensory processing during movement may contribute to differences in motor performance and learning during adolescence. However, the motor task in Chapter 3 was not designed to explore learning, so the results from the somatosensory experiments and the motor learning experiments are separate. There is evidence to suggest that changes occur in this somatosensory network during motor learning (Ostry et al., 2010). Future studies might benefit from exploring the somatosensory cortical oscillations during the motor learning paradigm, as these may also change with practice as individuals change how they process somatosensory feedback. Additionally, future studies should explore the effect of dosing on how the sensorimotor cortical oscillation change. We proposed in

Chapter 2 that the increase in power of the beta ERD in the adults may reflect that the adults were in the slow motor learning stage, while the adolescents were still in the fast motor learning stage. This supports the idea that adolescents need more trials to achieve motor learning similar to adults (Goh et al., 2012; Sullivan et al., 2008). However, we do not know how many trials would be needed for the adolescents to enter the slow motor learning stage. Building on this, a better understanding of how many trials each age group needs to achieve different motor learning stages may come from exploring tasks that adolescents would be practiced at that would be novel to adults. If the change in strength changed between groups for a task that the adolescents were more familiar with, it would provide strong evidence for our interpretation. Finally, future investigations need to explore how different a task need to be to be considered novel. If task familiarity can modulate the changes in the cortical oscillations, then this may affect results of motor learning studies. This phenomenon is somewhat known, as studies will exclude subjects likely to have experiences similar to the experimental task from motor learning studies that focus on learning a pattern with their fingers (Dumel et al., 2018; Gabitov et al., 2017; 2019; Gheysen et al., 2017; 2010, 2011), as these subjects have different activations that suggest they are in slow motor learning stages while the non-pianist subjects are in the fast motor learning stage (Hund-Georgiadis & von Cramon, 1999; Landau & D'Esposito, 2006; Perez et al., 2004). However, there is a knowledge gap surrounding how different a task would need to be so prior experience does not affect outcomes.

CONCLUSIONS

This dissertation explored the behavioral and neurophysiological changes that occur after practicing a motor task, how those changes might differ between adolescents and adults, and how the movement-related somatosensory response attenuation may differ between adolescents and adults. The outcomes of these studies identified that

adolescents and adults sensorimotor oscillatory activity does change differently after the same amount of practice and that adolescents attenuate their somatosensory responses a greater amount during movement. The results of these investigations added to the body of literature exploring the neurophysiologic changes associated with motor learning. This work provides new insights into how the neurophysiologic changes differ for adolescents and how the somatosensory feedback needed for motor learning may play a role. These results provide new insights into motor learning differences during adolescents and may be useful for designing motor learning strategies that are more advantageous for younger age groups.

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APPENDIX A: WHITE MATTER DEVELOPMENT IS UNRELATED TO THE SOMATOSENSORY AND MOTOR RESPONSES IN ADOLESCENTS

INTRODUCTION

Throughout typical development, adolescents demonstrate greater mastery of motor performance and somatosensory processing. For example, adolescents demonstrate greater mastery of single joint movements, drawing, aiming, reaching and grasping objects as they become older (Contreras-Vidal, 2006; Contreras-Vidal et al., 2005; Fayt et al., 1992; Hay et al., 1991; Jansen-Osmann et al., 2002; Kuhtz-Buschbeck et al., 1998; Yan et al., 2000). Further, behavioral studies have established that adolescents exhibit lesser haptic perceptions compared to adults (Angel & Malenka, 1982; Gori et al., 2012; Holst-Wolf et al., 2016; Milne et al., 1988). Although these are common behavioral findings, there is no consensus on why sensorimotor functions improve during this developmental stage.

There is considerable evidence that cortical regions involved with motor control and sensory processing change throughout adolescence. Structural MRI investigations show that the pre- and post-central gyri gray matter density greatly decrease in the first two decades of life, while overall white matter volume increases (Casey et al., 2008; Crone & Richard Ridderinkhof, 2011; Day et al., 2005; Marsh et al., 2008; Sowell et al., 2003). These white matter volume increases are often linked to improved cognitive performance (Bucur et al., 2008; Gold et al., 2007; Hale, 1990; Luna et al., 2004; Madden et al., 2004; Manoach et al., 2007; Nestor et al., 2007; Tuch et al., 2005; Westerhausen et al., 2006), as increased myelination helps to speed the transfer of information and cognitive processing speed (Luciano et al., 2004; Waxman, 1980). Therefore, structural changes of sensorimotor white matter tracts could be tied to the improving motor control seen throughout adolescence.

Additionally, there is ample evidence for differences in cortical function throughout adolescence. Outcomes from electroencephalography (EEG), MEG, and invasive electrocorticography (ECoG) experiments have shown that prior to the onset of movement cortical oscillatory activity in the beta frequency range (15-30 Hz) decreases, and this change is sustained throughout the majority of the movement (Gehringer et al., 2018; Heinrichs-Graham & Wilson, 2015; Jurkiewicz et al., 2006; Kilner et al., 2004; Kurz et al., 2017a; Miller et al., 2010; Pfurtscheller et al., 2003; Tzagarakis et al., 2010; Wilson et al., 2014; 2010; 2011). The consensus is that this beta ERD is related to the formulation of a motor plan, because it occurs well before the onset of movement and is influenced by the certainty of the movement pattern to be performed (Grent-'t-Jong et al., 2014; Heinrichs-Graham & Wilson, 2015; Tzagarakis et al., 2010; 2015). This pattern of activity has also been observed in adolescents. However, adolescents have a weaker beta ERD and recruit more brain regions when performing a motor action (Cheyne et al., 2014; Gaetz et al., 2010a; Kurz et al., 2016; Wilson et al., 2010). As for somatosensory oscillatory activity, it is well recognized that a peripheral stimulation while sitting quietly produces an immediate and transient synchronization (e.g., increase in power) across the 10-75 Hz frequency bands (Kurz et al., 2014a; 2015; 2017b; Wiesman et al., 2017). Chapter 3 of this dissertation demonstrated that there are differences in somatosensory cortical oscillations between adolescents and adults. These changes of the sensorimotor cortical activity, coupled with the structural changes during adolescence, suggest that changes in the brain effect the motor output of adolescents. However, the connection between these structural and functional changes is not fully understood.

Using the functional images created from MEG, it is possible to perform a seed-based analysis to explore the link between an oscillatory response and the white matter tracts that extend from the area of that response estimated by diffusion tensor imaging

(DTI; Fernández et al., 2011; Gaetz et al., 2010b; Jung et al., 2012; Kyousuke et al., 2007; Roberts et al., 2009; Stephen et al., 2013; Stufflebeam et al., 2008). A subset of these investigations have found connections between the amplitude or timing of sensory responses with related white matter structures (Jung et al., 2012; Roberts et al., 2009; Stephen et al., 2013; Stufflebeam et al., 2008). These investigations were able to find a connection between the function and structure of the brain, suggesting that these white matter tracts may be linked to the cortical oscillatory activity. However, this structure-function connection is largely unexplored in adolescents.

In the present study, we explore the connection between structure and function in typically developing adolescents. To do this, we used MEG to create seeds based on the oscillatory responses from an electrical stimulation to the tibial nerve and an ankle plantarflexion movement in adolescents for probabilistic DTI. Our key hypotheses were: 1) individuals with greater strength of the somatosensory cortical oscillations would have greater thalamocortical white matter tract integrity, and 2) individuals with greater strength of the sensorimotor cortical oscillations would have greater corticospinal white matter tract integrity.

METHODS

Subjects

The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation. Nineteen adolescents (Age = 14.8 ± 2.5 yrs.; Female = 9; Right handed = 19) and nineteen adults (Age = 36.8 ± 5.0; Female = 9; Right handed = 19) with no neurological or musculoskeletal impairments participated in the somatosensory portion of this investigation study. Seventeen healthy right-hand dominant adolescents (Mean Age = 14.0 yrs.; SD: ± 2.2 yrs., 8 female) with no neurological or musculoskeletal impairments participated in the motor portion of this

investigation. All of the participants or guardians provided written informed consent and the adolescents provided assent to participate in the investigation.

MR Acquisition

All scanning was performed on a Philips Achieva 3T X-series scanner. High-resolution T1-weighted sagittal images were obtained with an eight-channel head coil using a 3D fast field echo sequence with the following parameters: Field-of-view (FOV): 24 cm, 1 mm slice thickness, no gap, in-plane resolution of 1.0 x 1.0 mm, and sense factor of 2.0. The structural volumes were aligned parallel to the anterior and posterior commissures. DTI data was acquired with the following parameters: 64 non-collinear directions of gradient encoding (plus 2 b_0 volumes), TR/TE = 11,400/62 ms, FOV: 22.4 cm, 76 slices, voxel size: 2 x 2 x 2.25 mm, b-values = 1000.

MR Data Preprocessing

Each participant was subjected to automated segmentation and cortical parcellation of the T1w data using Freesurfer version 6.0.0. The standard Freesurfer "recon-all" was used. Subsequently, DTI data was preprocessed using Freesurfer "dt-recon" and the first two stages of the "trac-all" pipeline. The second stage of "trac-all" is FLS's "bedpostx" pipeline, which creates the files necessary to perform probabilistic tractography (Behrens et al., 2007).

MEG Data Acquisition

Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, the

participants were seated upright in a magnetically-silent chair and monitored via real-time audio-video feeds from inside the shielded room during the experiment.

MEG Somatosensory Paradigm

The participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. Unilateral electrical stimulation was applied to the right posterior tibial nerve using external cutaneous stimulators that were connected to a Digitimer DS7A constant-current stimulator system (HW Medical Products, Neuberg, Germany). During stimulation, each participant sat quietly focused on a fixation cross (passive condition). During both the passive and active conditions, single 0.2 ms constant current square waves were presented using an interstimulus interval that randomly varied between 1800 and 2200 ms. The amplitude of the pulses was set to the threshold required to elicit a visible flexor twitch in the hallux.

MEG Motor Control Paradigm

A custom-built, magnetically-silent force transducer was developed for this investigation to measure isometric ankle plantarflexion forces. This device consisted of a 20 x 10 cm air bladder that was inflated to 317 kPa and was integrated within an ankle foot orthosis. Changes in the pressure of the airbag, due to participants' generating an isometric ankle plantarflexion force, were quantified by an air pressure sensor (Phidgets Inc., Calgary, Alberta, CA) and were converted into units of force offline.

The experimental paradigm involved the participant generating an isometric ankle plantarflexion force with their right leg that matched target forces that varied between 15-30% of the participant's maximum isometric ankle plantarflexion force. The step size between the respective targets was one unit of force. The target force was visually displayed as a moth, and the force generated by the participant was shown as a frog that was animated vertically, based on the isometric force generated. The participants were instructed to match the presented targets as fast and as accurately as possible. The

distinct target forces were presented in a random order, and a successful match occurred when the bug that represented the target force was inside the frog's mouth for 0.3 s. The stimuli were shown on a back-projection screen that was approximately ~1 meter in front of the participant and at eye-level. Each trial was 10 s in length. The participants started each trial at rest while fixating the center of the screen for 5 s. After this rest period, the target would appear, prompting the participant to try and produce the matching force value. The target was available to be matched for up to 5 s. Once the target was matched or 5 s elapsed, feedback was given to indicate the end of the trial, and the participant returned to rest and fixated on the center of the screen while waiting for the next target to appear. Participants performed three blocks of the ankle plantarflexion target-matching task, with each block containing 100 trials. The first and third blocks were performed while recording MEG data, while the second block acted as an extended practice block, where the participant was provided additional information about the accuracy of their target matching performance via an interactive biofeedback program. This program showed the participant the amount of error in their motor action by displaying the distance between the bug and the frog and provided auditory and visual rewards when the participant matched the target faster and had improved accuracy.

MEG Coregistration

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (*e.g.*, 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed for each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in

head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered to a structural MRI (MPRAGE) using three external landmarks (*i.e.*, fiducials), and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures, and all data were transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

Using the MaxFilter software (Elekta), each MEG data set was individually corrected for head motion that may have occurred during the task performance, and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Artifact rejection was based on a fixed threshold method, supplemented with visual inspection.

MEG Somatosensory Pre-Processing

The continuous magnetic time series was divided into epochs of 1100 ms in duration (-500 to 600 ms), with the onset of the electrical simulation defined as 0 ms and the baseline defined as -200 to 0 ms. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation and averaged over the respective trials. These sensor-level data were normalized by dividing the power value of each time-frequency bin by the respective bin's baseline power, which was calculated as the mean power during the baseline (−200 to 0 ms).

MEG Motor Pre-Processing

The continuous magnetic time series was divided into epochs of 10.0 s in duration (-5.0 s to +5.0 s), with the onset of the isometric force defined as 0.0 s and the baseline defined as -2.0 to -1.4 s. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation (resolution: 2.0 Hz, 0.025 s) and averaged over the respective trials. These sensor-level data were normalized using the

respective bin's baseline power, which was calculated as the mean power during the baseline (−2.0 to -1.4 s).

Time-Frequency Transformation

The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Briefly, each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point, and the output spectrogram of t-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants and conditions. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also below the ($p < 0.05$) threshold and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values, and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris & Oostenveld, 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

MEG Source Imaging

A minimum variance vector beamforming algorithm was employed to calculate the source power across the entire brain volume (Gross et al., 2001). The single images were derived from the cross spectral densities of all combinations of MEG sensors and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth to the

target periods that were identified through the sensor-level statistical analyses (see above; Hillebrand & Barnes, 2005; Hillebrand et al., 2005; Van Veen et al., 1997). Thus, the normalized power per voxel was computed over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. MEG pre-processing and imaging used the Brain Electrical Source Analysis (BESA) software (BESA v6.0; Grafelfing, Germany).

Time series analysis was subsequently performed on the peak voxels extracted from the grand-averaged beamformer images (see Results). The virtual sensors were created by applying the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which resulted in a time series with the same temporal resolution as the original MEG recording (Cheyne et al., 2006; Heinrichs-Graham et al., 2016; Heinrichs-Graham & Wilson, 2016). Once the virtual sensors were extracted, they were transformed into the time-frequency domain, and the two orientations for each peak voxel per individual were combined using a vector-summing algorithm. The power of these time courses, relative to baseline, was averaged across the window of interest for each individual to assess group and practice differences in the key oscillatory responses.

DTI Seed-Based Analysis

The preprocessed DTI was subjected to FSL's probtrax2 processing pipeline. For the somatosensory responses, the source seed was set as the source localized somatosensory response, with the termination and waypoint seed set as the thalamus, as defined in MNI space by the Harvard-Oxford Subcortical Structural Atlas. For the motor response, the source seed was set as the sensorimotor MEG cluster and the termination and waypoint seed was the brain stem, as defined in MNI space by the Harvard-Oxford Subcortical Structural Atlas. Waypoint seeds were added so that only tracts that connected to the termination seeds were included.

Average FA and MD Calculation

Once all the probabilistic tracts were calculated, they were then turned into a binary mask and applied to the FA and MD maps created by Freesurfer. The resulting masked images were then averaged using FSLMaths.

Statistics

SPSS version 22 (IBM, Armonk, NY) was used to test correlations between average FA/MD values and the average powers and peak latency of the sensorimotor responses from the time series. Spearman's rank order correlations were ran to test for possible connections between the MEG responses and the white matter integrity. False discovery rate (FDR) was used to correct the alpha values for multiple comparisons (Benjamini & Hochberg, 1995).

RESULTS

Somatosensory Sensor-Level Results

Significant oscillations were detected in a cluster of gradiometers near the fronto-parietal region. The sensor-level spectrograms revealed significant alpha-beta (8-30 Hz) event related synchronizations (ERS) that were initiated immediately after the stimulation and were sustained for 125ms ($P < 0.0001$, corrected).

Alpha-Beta Event-Related Synchronization

The beamforming of the alpha-beta (8-30 Hz) ERS within the 0 to 125 ms time window was also performed using a baseline period of −150 to -25 ms. The alpha-beta ERS was centered in the leg region of the contralateral somatosensory cortex and was used for the source seed for the thalamocortical tracts (Figure 19). The local maximums seen in this cortical area were subsequently used to extract the virtual time courses each participant, and the average activity across the 0 to 125 ms time window was subsequently calculated.

Somatosensory Functional/Structural Correlations

The Spearman's rank order correlations did not find any significant correlations between the average power of the somatosensory responses and the FA or MD values, after being corrected for multiple comparisons using FDR. Additionally, the Spearman's rank order correlations did not find any significant correlations between the somatosensory peak response time and the FA or MD values, after being corrected for multiple comparisons using FDR.

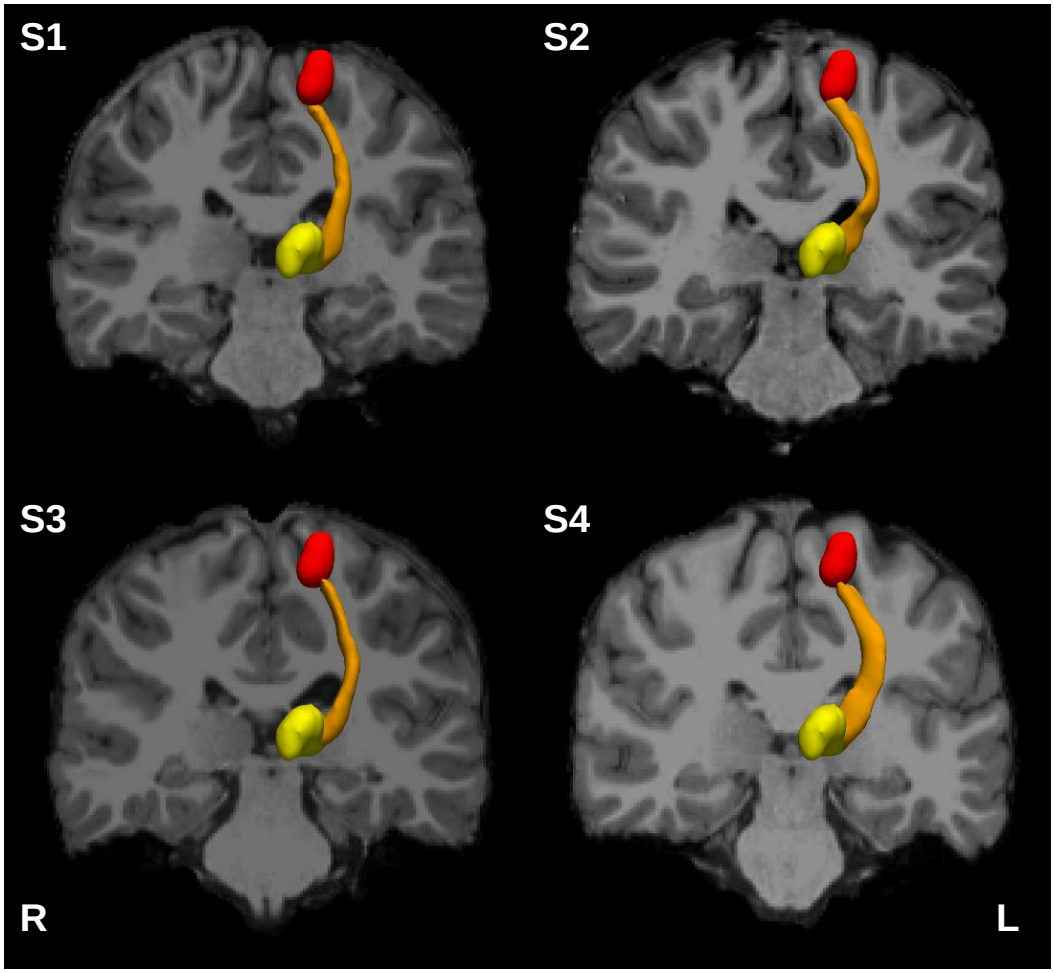

Figure 19: Exemplary Thalamocortical Tracts. These tracts were generated using the somatosensory response measured by the MEG (in red) as a source seed and the thalamus (in yellow) as the termination and waypoint seed. These demonstrate the tracts generated with FSL (in orange) thresholded above 20% of their maximum and overlayed on the subjects anatomy transformed into MNI space. Figures are presented in radiological space (R = L).

Motor Sensor-Level Results

When collapsing the data across the respective blocks (pre- and post-practice), there was a significant beta (18-32 Hz) ERD that was present in a large number of sensors near the

fronto-parietal region (P < 0. 0001, corrected). The responses in the beta band started about 0.3 s before movement onset and were sustained for approximately 0.6 s afterward.

Beta Oscillations Event-Related Desynchronization

The beta (18-32 Hz) ERD identified in the sensor-level analysis between -0.3 and 0.3 s was imaged using a beamformer. This analysis combined the data acquired across the respective pre-/post-practice blocks and used a baseline period of −2.0 to -1.4 s. The resulting images were grand-averaged across pre-/post-practice blocks and indicated that the beta ERD was more centered on the leg region of the sensorimotor cortices. This

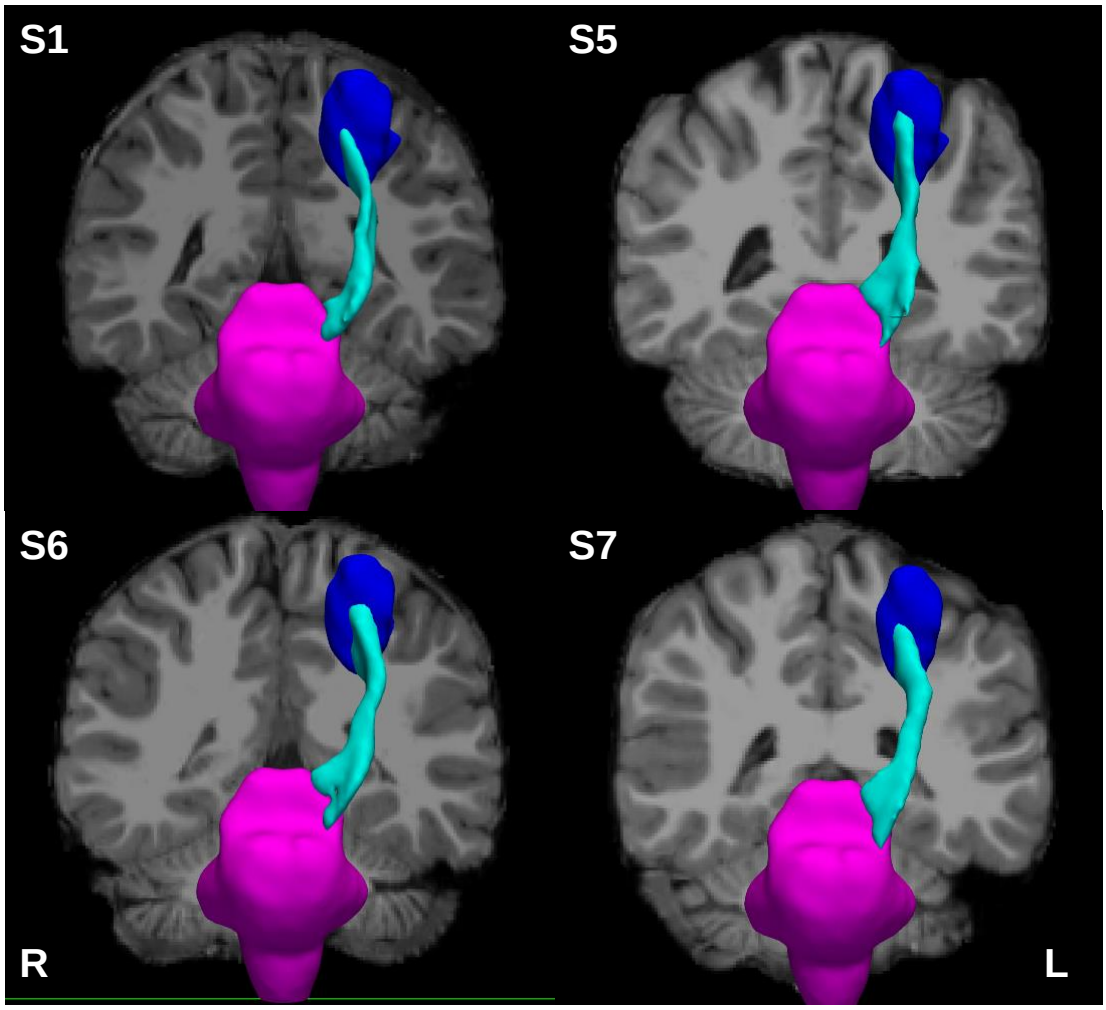

Figure 20: Exemplary Corticospinal Tracts. These tracts were generated using the sensorimotor response measured by the MEG (in blue) as a source seed and the brain stem (in purple) as the termination and waypoint seed. These demonstrate the tracts generated with FSL (in cyan) thresholded above 20% of their maximum and overlayed on the subjects anatomy transformed into MNI space. Figures are presented in radiological space (R = L).

cluster was used as a source seed for the corticospinal tracts (Figure 20). The local maximums of these responses were next used as seeds for extracting virtual sensors from the pre and post-practice data blocks separately (per participant).

Motor Structural/Functional Correlations

The Spearman's rank order correlations did not find any significant correlations between the average power of the motor responses and the FA or MD values, after being corrected for multiple comparisons using FDR. Additionally, the Spearman's rank order correlations did not find any significant correlations between the motor peak response time and the FA or MD values, after being corrected for multiple comparisons using FDR.

DISCUSSION

This investigation used MEG and DTI to quantify the connection between the sensorimotor cortical oscillations and the integrity of the associated white matter tracts in adolescents. The data-driven approach employed in this investigation revealed an alpha-beta ERS (8-30 Hz, 0-125 ms) for the somatosensory response to a peripheral stimulation on the tibial nerve and a beta ERD (18-32 Hz, -300 – 300 ms) for the ankle plantarflexion task. These responses were then subjected to a beamformer and the grand average images were used as seeds for probabilistic tractography. Once these thalomocortical and corticospinal tracts were estimated, the FA and MD values of these tracts were extracted and used to investigate the correlation between structure and function. However, there were no significant correlations between the FA or MD values of the thalamocortical tract and the power of the somatosensory response. Additionally, there were no significant correlations between the FA or MD values of the corticospinal tract and the power of the motor response. Further tests were ran to investigate the correlation between the FA or MD values of these tracts and the timing of the peak of these responses. Again, there were no significant correlations between the FA or MD values of the thalamocortical tract

and the latency of the peak of the somatosensory response. Likewise, there were no significant correlations between the FA or MD values of the corticospinal tract and the latency of the peak of the motor response.

Previous investigations have found relationships between the white matter integrity and the amplitude of a response (Jung et al., 2012; Stephen et al., 2013). One of these studies used joint independent component analysis to identify sources from an auditory and visual sensory integration task (Stephen et al., 2013). This investigation found significant correlations between the auditory component and temporal association tracts and the occipital source and anterior/posterior association tracts. The other investigation used a haptic exploration paradigm to explore the relationship between the somatosensory responses and the white matter integrity of the tracts between these responses. Their primary finding was a significant relationship between the FA of callosal fibers interconnecting the secondary somatosensory cortices and the interhemispheric inhibition (Jung et al., 2012). While this investigation did analyze the connections to the primary somatosensory responses, there were no findings that involved that oscillatory response or the thalamococortical tracts.

Furthermore, investigations have found relationships between the white matter integrity and the latency of a response (Roberts et al., 2009; Stufflebeam et al., 2008). This relationship is often investigated as the increases in the speed of information processing that comes from increased myelination is connected to improved performance in cognitive tasks (Bucur et al., 2008; Gold et al., 2007; Hale, 1990; Luna et al., 2004; Madden et al., 2004; Manoach et al., 2007; Nestor et al., 2007; Tuch et al., 2005; Westerhausen et al., 2006).The first of these MEG-DTI studies found significant correlations between the auditory-evoked responses, age, and FA values of the acoustic radiations in adolescents (Roberts et al., 2009). The other study found a correlation

between visual evoked responses and the FA values in the posterior parietal cortex and frontal eye fields (Stufflebeam et al., 2008). However, the subjects in this investigation were 8 typically developed adults. Additionally, the tracts explored in these investigations are often thought to mature later than the thalamocortical and corticospinal tracts (Wilkinson et al., 2017).

Given the small subset of combined MEG-DTI papers that found connections between the amplitude or latency of a response and the FA/MD, it is not surprising that the results in the present investigation found no significant correlations. While white matter tract development extends into the third decade of life, the thalamocortical and corticospinal tracts mature earlier than other sensory-related tracts and are mostly mature by adolescence (Asato et al., 2010; Eluvathingal et al., 2007; Wilkinson et al., 2017). Further, the size of the brain is considered nearly adult-like by 3 years of age, with some structural studies only looking at differences between those younger than and older than 3 years of age (Berchicci et al., 2011; Cohen et al., 2016; Gredebäck & Kochukhova, 2010; Lippé et al., 2009; Thompson, 2001; Wilkinson et al., 2017). Considering the age range (11 – 17 years) and the tracts selected for the present investigation, it is likely that these data did not encapsulate a large enough age range to identify development-based changes of the thalamocortical or corticospinal tracts.

CONCLUSIONS

This investigation did not find a connection between the power or latency of the somatosensory or motor responses and the average FA/MD of the thalamocortical or corticospinal tracts, respectively. As the thalamocortical and corticospinal tracts are thought to be mostly developed by adolescence, there may not be any appreciable change in the FA/MD values across our subjects. We suggest that future studies include a larger

age group, ranging from around 3 years to 25 years, in order to see a larger change across lifespans.

APPENDIX B: CURRICULUM VITAE

James Gehringer, B.S.

Date: 4/2011-5/2012
Position: Student Researcher
Institution: University of Nebraska Omaha
Lab PI: Allison Baysa
Brief Project Description: Collaborated with STRATCOM (United States Department of Defense) engineers on a multidisciplinary team to help advance the usability of their 3D Virtual world software as a tester and developer.

1. Oerter J, Suddarth W, Morhardt M, **Gehringer JE**, McGinnis ML, Shockley J, and Baysa A. A system architecture and simulation environment for building information modeling in virtual worlds. 2013. The Journal of Defense Modeling and Simulation: Applications, Methodology, Technology. 11: 205-210.

Date: 5/2013-4/2014
Position: Research Assistant
Institution: University of Nebraska Medical Center
Lab PI: Max Kurz, Ph.D.
Brief Project Description: Developed hardware and software for research paradigms and helped with data collections exploring the motor control activity in children with cerebral palsy.

1. Arpin DJ, Kurz MJ, **Gehringer JE**, & Wilson TW (2014). Abnormal Cortical Oscillations in Children with Cerebral Palsy during a Target Matching Knee Extension Task. Proceeding of the Nebraska Neuroscience Symposium, Omaha, Nebraska.
2. Arpin DJ, **Gehringer, JE**, & Kurz, MJ (2014). Synchronization of the Cortical Oscillations in the Beta Frequency Range during Movement. Proceeding of the Nebraska Academy of Science Meeting, Lincoln, Nebraska.
3. Davies, BL, **Gehringer, JE**, & Kurz, MJ (2014). Motor planning as a biomarker for sensorimotor integration difficulties in astronauts after spaceflight. Presented at the 124th Nebraska Academy of Sciences Annual Meeting, Lincoln, NE, USA.

Date: 5/2014-Present
Position: Graduate Research Assistant (full-time)
Institution: University of Nebraska Medical Center
Lab PI: Max Kurz, Ph.D.
Brief Project Description: Conduct experiments focusing on the neuroimaging of motor control, motor learning, and somatosensory systems in populations with motor learning deficits, while continuing the hardware and software development for research paradigms and data processing for our laboratories.

Publications

1. Davies BL, **Gehringer JE**, Kurz MJ. Age-related differences in the motor planning of a lower leg target matching task. Human Movement Science. 2015;44:299-306.
2. Kurz MJ, Arpin DJ, Davies BL, **Gehringer JE**. Dissipation of disturbances seen in the knee joint kinematics of children with cerebral palsy. Acta Bioengineering and Biomechanics. 2015;17(4):67-72.

3. Kurz MJ, Proskovec AL, **Gehringer JE**, Becker KM, Arpin DJ, Heinrichs-Graham E, Wilson TW. Developmental trajectory of beta cortical oscillatory activity during a knee motor task. Brain Topography, 2016;29(6):824-833.
4. Heinrichs-Graham E, Kurz MJ, **Gehringer JE**, Wilson TW. The functional role of post-movement beta oscillations in movement termination. Brain Structure and Function. 2017;222(7):3075-3086.
5. Wiesman AI, Heinrichs-Graham E, Coolidge NM, **Gehringer JE**, Kurz MJ, Wilson TW. Oscillatory dynamics and functional connectivity during gating of primary somatosensory responses. The Journal of Physiology. 2016;595(4):1365-1375.
6. Kurz MJ, Proskovec A, **Gehringer JE**, Heinrichs-Graham E, Wilson TW. Children with cerebral palsy have altered oscillatory activity in the motor and visual cortices during a knee motor task. NeuroImage: Clinical. 2017;15:298-305.
7. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Zabad R, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Human Brain Mapping. 2017;38(8):4009-4018.
8. Arpin DJ, **Gehringer JE**, Wilson TW, Kurz MJ. A reduced somatosensory gating response in individuals with multiple sclerosis is related to walking impairment. Journal of Neurophysiology, 2017;118(4):2052-2058. Selected for APSselect, September 2017.
9. Arpin DJ, **Gehringer JE**, Wilson TW, Kurz MJ. Movement-related somatosensory attenuation is altered in patients with multiple sclerosis: MEG evidence of impaired sensorimotor integration. Brain Topography. 2018, 31(4):700-707.
10. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neurophysiological changes in the visuomotor network after practicing a motor task. Journal of Neurophysiology, 2018;120(1):239-249.
11. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Practice modulates motor-related beta oscillations differently in adolescents and adults. The Journal of Physiology, 2018, Under Review.
12. VerMaas JR, **Gehringer JE**, Wilson TW, Kurz MJ. Children with cerebral palsy display altered visual perceptions and neural oscillations within the visual MT/V5 cortices. NeuroImage: Clinical. 2018, Under Review.

Refereed Abstracts

1. **Gehringer JE**, and Kurz MJ. Mechanical Work Performed By the Legs of Children with Hemiplegic Cerebral Palsy. 2015 Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2015.
2. **Gehringer JE**, and Kurz MJ. Mechanical Work Performed By the Legs of Children with Hemiplegic Cerebral Palsy. 2015 National American Society of Biomechanics Conference, Columbus, Ohio, August 2015.
3. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.
4. Sukar S, Hoffman R, Davies BL, **Gehringer JE**, Harbourne R, Kurz MJ. Planning sequential motor actions in children with hemiplegic cerebral palsy. Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.
5. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a

faulty internal model. Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.

6. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. 2016 Society for Neuroscience Annual Conference, San Diego, California, November 2016.
7. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. 2016 Society for Neuroscience Annual Conference, San Diego, California, November 2016.
8. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. The Effect of Cerebellar tDCS on Lower Extremity Motor Learning. 127th Nebraska Academy of Sciences Annual Meeting, Lincoln, NE, USA, April 2017.
9. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Beta oscillations during movement execution in the sensorimotor cortex change after practicing a motor task. The 21st International Conference on Biomagnetism, Philadelphia, PA, USA, August 2018
10. **Gehringer JE**, Arpin DJ, Wilson TW, Kurz MJ. Self-reported Pain Levels are Related with the Aberrant Somatosensory Activity in Children with Cerebral Palsy. American Academy of Cerebral Palsy 72nd Annual Meeting, Cincinnati, OH, USA, October 2018

Podium Presentations

1. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Podium presentation, Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.
2. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Podium presentation, Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.
3. VerMaas JR, **Gehringer JE**, Wilson TW, Kurz MJ. Visual Motion Perception Is Aberrant in Children With Cerebral Palsy. Podium presentation, American Occupational Therapy Association Annual Conference and Expo, New Orleans, Louisiana, April 2019.
4. **Gehringer JE**, Hoffman RM, Baker SE, Wilson TW, Kurz MJ. Aberrant Beta Sensorimotor Cortical Oscillations are related with the Altered Gait Kinematics seen in Adolescents with Cerebral Palsy. American Academy of Cerebral Palsy 73rd Annual Meeting and International Alliance of Academies of Childhood Disability 2nd Triannual Meeting, Anaheim, CA, USA, September 2019

Poster Presentations

5. **Gehringer JE**, and Kurz MJ. Mechanical Work Performed By the Legs of Children with Hemiplegic Cerebral Palsy. Poster presentation, 2015 Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2015.
6. **Gehringer JE**, and Kurz MJ. Mechanical Work Performed By the Legs of Children with Hemiplegic Cerebral Palsy. Poster presentation, 2015 Munroe-

Meyer Institute Annual Student & Faculty Research Poster Session, Omaha, Nebraska, April 2015.

7. **Gehringer JE**, and Kurz MJ. Mechanical Work Performed By the Legs of Children with Hemiplegic Cerebral Palsy. Poster presentation, 2015 National American Society of Biomechanics Conference, Columbus, Ohio, August 2015.
8. Sukar S, Hoffman R, Davies BL, **Gehringer JE**, Harbourne R, Kurz MJ. Planning sequential motor actions in children with hemiplegic cerebral palsy. Poster presentation, Rocky Mountain Regional American Society of Biomechanics Conference, Estes Park, Colorado, April 2016.
9. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Poster presentation, 2016 Munroe-Meyer Institute Annual Student & Faculty Research Poster Session, Omaha, Nebraska, April 2016.
10. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Poster presentation, 2016 Munroe-Meyer Institute Annual Student & Faculty Research Poster Session, Omaha, Nebraska, April 2016.
11. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Poster presentation, 2016 Society for Neuroscience Annual Conference, San Diego, California, November 2016.
12. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Poster presentation, 2016 Society for Neuroscience Annual Conference, San Diego, California, November 2016.
13. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Poster presentation, 2016 Munroe-Meyer Institute Annual Student & Faculty Research Poster Session, Omaha, Nebraska, April 2016.
14. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Poster presentation, 2016 Munroe-Meyer Institute Annual Student & Faculty Research Poster Session, Omaha, Nebraska, April 2016.
15. Sukar S, Hoffman R, Davies BL, **Gehringer JE**, Harbourne R, Kurz MJ. Planning sequential motor actions in children with hemiplegic cerebral palsy. Poster presentation, Nebraska EPSCoR Symposium on Biomechanics, Omaha, Nebraska, October 2016.
16. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Neuromechanical changes associated with learning an isometric ankle plantarflexion target matching task. Poster presentation, Nebraska EPSCoR Symposium on Biomechanics, Omaha, Nebraska, October 2016.
17. Arpin DJ, Heinrichs-Graham E, **Gehringer JE**, Wilson TW, Kurz MJ. Altered sensorimotor cortical oscillations in individuals with multiple sclerosis suggests a faulty internal model. Poster presentation, Nebraska EPSCoR Symposium on Biomechanics, Omaha, Nebraska, October 2016.
18. **Gehringer JE**, Arpin DJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Beta oscillations during movement execution in the sensorimotor cortex change after practicing a motor task. The 21st International Conference on Biomagnetism, Philadelphia, PA, USA, August 2018

19. **Gehringer JE**, Arpin DJ, Wilson TW, Kurz MJ. Self-reported Pain Levels are Related with the Aberrant Somatosensory Activity in Children with Cerebral Palsy. American Academy of Cerebral Palsy 72nd Annual Meeting, Cincinnati, OH, USA, October 2018

Academic and Professional Honors

Walter J. Scott's Scholarship 2010-2014
Nebraska Regents Scholarship 2010-2014
Capstone Conference Award for Best Senior Project in Computer and Electronics Engineering Department
B.S. Awarded, University of Nebraska Lincoln, 2014
UNeMed New Invention Notification Contributor 2014
National Science Foundation Graduate Research Fellowship Program Honorable Mention 2015
Nebraska NASA Fellowship Recipient 2016
University of Nebraska Medical Center Graduate Studies Research Fellowship 2016-2018
Nebraska State Soccer TOPSoccer Coach of the Year 2016
Purdue Pharma Scholar 2017
Selected for APSselect showcase in September 2017 for the article "A reduced somatosensory gating response in individuals with multiple sclerosis is related to walking impairment"
American Academy of Cerebral Palsy and Developmental Medicine Student Travel Scholarship 2018

Memberships in Professional Societies

American Society of Biomechanics
Institute of Electrical and Electronics Engineers
Society for Neuroscience
American Academy of Cerebral Palsy and Developmental Medicine