UNDERSTANDING THE NEUROPHYSIOLOGY OF ACTION INTERPRETATION IN RIGHT AND LEFT-HANDED INDIVIDUALS

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Rachel Louise Kelly

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“You can never cross the ocean until you have the courage to lose sight of the shore.”
-Christopher Columbus

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Approved by:

Dr. Lewis A. Wheaton, Advisor
School of Applied Physiology
Georgia Institute of Technology

Dr. J. C. Mizelle
Center for Visual and Neurocognitive Rehabilitation
Atlanta Veterans Affairs Medical Center

Dr. T. Richard Nichols
School of Applied Physiology
Georgia Institute of Technology

Dr. Boris I. Prilutsky
School of Applied Physiology
Georgia Institute of Technology

Dr. Teresa Snow
School of Applied Physiology
Georgia Institute of Technology

Date Approved: March 13, 2015

To my family, whom this was only possible because of their guidance, love and dedicated partnership for success in my life.

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SUMMARY

Investigating the neurophysiology behind our action encoding system offers a way of probing the underlying mechanisms regarding how we understand seen action. Being able to understand seen action is important for understanding the intent of others. The ability to mentally simulate action (motor simulation) is a strong theory for how we interpret others' actions. Motor simulation is the capability to observe an action in another individual and re-enact that same action either through actual motion or mental rehearsal. The process of how we generate accurate motor simulations is proposed to be reliant on the task and object pair along with sensory feedback from the limb. However, the neurophysiological mechanisms behind motor simulation are not yet understood. The objective of this dissertation is to further identify the underlying neurophysiology of the motor simulation theory to gain insight into the strategy of how we interpret action.

Based on known motor physiology for right-handed individuals, there is a left hemispheric parietal-frontal network for the planning and execution of skilled movements (action encoding). This left-lateralized network is also active for motor simulation of the same movements (motor simulation). The execution of movements and action simulation has been focused primarily on right-handed individuals, with hypotheses that motor resonance would engage neural processes in the right hemisphere for left-handed individuals. Without the knowledge of what occurs in left-hand dominant individuals, we cannot infer that the left parietal-frontal network is solely responsible for action encoding and motor simulation in all people. Further, it remains unclear whether the laterality of networks for motor simulation in right handed people may occur outside of the motor

dominant hemisphere for left-handed people, which may create asymmetry between action encoding and the observer's motor system in different groups. In other words, it is uncertain whether the left hemispheric location of this network is due to right limb dominance of the observer's motor system. It is possible that motor simulations engage the motor dominant hemisphere due to a mapping of all seen actions (regardless of which limb is seen) to the dominant (right) limb. Another possibility is that regardless of which limb is seen, the left hemisphere is specialized for simulating action. The goal of this dissertation was to identify the underlying neurophysiology of the motor simulation process during action encoding in right and left hand dominant individuals. Generally, we hypothesize different strategies of action simulation between right and left-handed individuals. More specifically, we proposed that right-handed individuals would rely on their motor dominant left hemisphere for action encoding and motor simulation, while left-handed individuals would have a symmetrical pattern in their dominant right hemisphere.

First, this dissertation showed that there was a behavioral effect on action interpretation when different perspectives and hands were viewed based on motoric dominance. These findings demonstrated that action outcomes are best facilitated in an egocentric perspective and that motoric dominance influences action interpretation in an allocentric perspective. Next, cortical networks were evaluated between left and right-handed individuals to determine the laterality of brain activity when interpreting action images. A distinct pattern in laterality between participant groups was observed that corresponded to a pattern of "mirror-matched mappings." For right-handed individuals, this suggested they had a distinct motor lateralization based on the perspective and hand

seen in the action image. In the egocentric perspective, lateralization of networks were dependent on a limb matched mapping strategy and in the allocentric perspective, subjects utilized a mirror matched strategy. Left-handed individuals had a different motor lateralization pattern which showed regardless of the limb seen in a particular perspective, they always showed bilateral patterns of lateralization. Next, cortico-muscular coherence was evaluated to understand the reasons why we observed the laterality patterns in the previous study, to further identify if a neuromuscular strategy exists for action understanding. For both right and left-handed individuals, there was a decrease in cortico-muscular coherence to the hand the participant was mapping the action to, which aligned to the motor lateralization of the prior study. This finding demonstrates that seen actions are self-driven in an internal perspective and indicate a distributed pattern of how actions are mapped onto oneself. These networks are dependent on which limb, dominant or non-dominant, is seen. Finally, the deprivation sensory feedback to the dominant limb and identifying how that effects action interpretation was investigated. When sensory feedback is reduced, the limb mapping strategy used for action interpretation is altered, and therefore alters the neural networks to accommodate for the perturbation.

The results of this series of studies fill a void in our basic understanding of the motor simulation process and may generalize to populations with upper limb functional loss. This loss can occur after a stroke, amputation or disease, and may cause the inability to perform daily activities needed for independent living. Depending on which limb (dominant or non-dominant) is affected, motor simulation based rehabilitation programs may need to more carefully consider visual perspective and handedness to optimize

outcomes. The concept of mental simulations has been used as a component of motor recovery in rehabilitation (Braun et al., 2013). Studies have shown that mental simulation do not actually produce overt movement (motor imagery) can generate sensory input (Porro et al., 1996). Motor simulations happen when an internal representation of a specific movement is simulated vividly in the mind and the person can perceive themselves executing it. Mental rehearsal of performing a task is a low cost rehabilitation strategy that increases patient practice without the supervision of a therapist. While motor imagery has been shown to be a potential tool to improve motor function, little is known about the underlying physiology of the process. Through identifying neural networks and corresponding neuromuscular strategies during action observation and motor simulation, we proposed a neurophysiological model for action understanding.

CHAPTER 1

INTRODUCTION

Problem Definition

Upper limb functional loss is the loss of motor and/or sensory function that can occur in either or both arms and is caused by stroke, trauma, or disease. The loss of upper limb function can be devastating, particularly when the hand is involved, and can leave individuals unable to perform simple daily activities without assistance. Upper limbs are essential in daily activities such as feeding, using the restroom and dressing. Additionally, upper limbs are needed for mobility in sit to stand movements, balance during walking, or when using crutches or a wheelchair. The inability to perform these activities greatly impacts a patient's level of independence. Restoring the function of the upper limbs is complex and often remains limited (Lai, Studenski, Duncan, & Perera, 2002). Action Observation (AO) therapy is a neurophysiological rehabilitation method that utilizes an observers' ability to simulate actions and action outcomes from observing motor tasks (motor simulation). When a person observes an action being performed, the same neural structures responsible for the execution of that action are being activated in the person perceiving the action (Jeannerod, 1995). This mechanism follows the well-known theory that performing and observing an action activates common neural processes, via the mirror neuron system (Rizzolatti & Craighero, 2004). AO has been used in the recovery of upper limb functional loss. During AO therapy, a patient watches someone perform daily actions in a video clip, which drives a motor simulation, and then they execute the action themselves (Bellelli, Buccino, Bernardini, Padovani, & Trabucchi, 2010; Buccino et al., 2012). For amputees the protocol is similar, with the exception that they are performing the action with their new prosthetic device (Cusack et al., 2012a). However, the neurophysiological mechanisms behind motor simulations are not yet understood. The objective of this research is to understand the underlying neurophysiology of motor simulation theory to gain insight into the strategy of how we interpret action.

Based on known motor physiology for right-handed individuals, there is a left parietal-frontal network for the planning and execution of skilled movements (action encoding). This left-lateralized network is also active for motor simulation of the same movements. However, it remains unclear whether the left hemispheric location of this network is due to right limb dominance of the observer's motor system. Studies showing the left-lateralized network often only include right-handed subjects and exclude left-handed subjects altogether (Willems, Van der Haegen, Fisher, & Francks, 2014). It is possible that motor resonance engages the left hemisphere for mapping of all seen actions. This would suggest that in left-handed individuals, the opposite would occur, motor resonance engages the right hemisphere due to a mapping of all seen actions (regardless of which limb is seen) to the dominant (left) limb. Another possibility is that regardless of the hand dominance of the individual, the left hemisphere is specialized for simulating action. Prior work on action simulation has been focused primarily on right-handed individuals due to anatomical variations in the cortex (Janssen, Meulenbroek, & Steenbergen, 2011), with hypotheses that motor resonance would engage neural processes in the right hemisphere for left-handed individuals. Without exploring the hypothesis of what occurs in left-hand dominant individuals, we cannot infer that the left parietal-frontal network is solely responsible for action encoding and motor simulation in all people. Further it remains unclear whether the laterality of networks for motor simulation may occur outside of the motor dominant hemisphere, which may create asymmetry between action encoding and the observer's motor system.

The question this dissertation addresses is: are there neural and neural-muscular circuits that can identify a network used for action understanding in both left- and right-handed individuals? This will be done by manipulating hand dominance, perspective, and hand seen to probe the behavioral, cortical, and muscular strategies used during action understanding. The central hypothesis of this work is: depending on the perspective and hand seen in an action image, there will be a lateralized neurophysiological circuit used for action understanding. The results of this series of studies will fill a void in our basic understanding of the motor simulation process and may generalize to populations with disorders influencing their neural control of movement. More specifically, hand dominance and perspective may impact rehabilitation programs designed to retrain an affected limb.

Research Aims

Specific Aim #1

Question

How does visual perspective and handedness interact in order to affect the identification of an action goal in a tool use motor task?

Aim

To evaluate the behavioral effects on action encoding for different perspectives and hands viewed.

Hypothesis

Action interpretation will occur best in an egocentric perspective; however, when viewing stimuli in an allocentric perspective, identification of action will occur best for a mirror-matched dominant limb for all participants.

Approach

Understanding handedness affords the opportunity to identify the role of mirroring and matched limb action encoding, which may display unique strategies of action understanding. Using behavioral data collection, latency and accuracy were recorded is to evaluate how perspective and handedness interact to understand and identify tool action outcomes.

Specific Aim #2

Question

Are there differences in cortical network patterns between left- and right-handed individuals when identifying action goals?

Aim

Determine if there is a difference in laterality of brain activity that can be seen for left- and right-handed participants when judging different action images.

Hypothesis

Right-handed participants will have left lateralized parietal-premotor networks when looking at right-handed egocentric images, and right lateralized activations when looking at left-handed egocentric images which suggests a direct limb match (as opposed to always mapping to the dominant limb). However, for allocentric images, they will have left lateralized cortico-cortical coherence regardless of hand being perceived.

Left-handed participants will have bilateral activation regardless of perspective in the parietal-premotor network due to a dissociation of tool-use knowledge and hand dominance.

Approach

Using electroencephalography (EEG), cortical-cortical coherence patterns were evaluated to determine if a distinct pattern in laterality could be observed between right and left-handed participants that were dependent on limb viewed.

Specific Aim #3

Question

Does brain to muscle communications reveal laterality patterns that suggest a neuromuscular mechanism of action observation?

Aim

Evaluate brain to muscle networks to determine if a neuromuscular strategy exists for motor simulations during action understanding.

Hypothesis

There will be a modulation in cortico-muscular coherence corresponding with the hand the participant is mapping to. In egocentric perspectives there will be left cortico-muscular coherence decrease when viewing a left hand and a right cortico-muscular coherence decrease when viewing a right hand. In the allocentric perspective, decrease patterns of cortico-muscular coherence will follow a mirror-matched limb strategy.

Approach

This aim utilized both EMG and EEG, which was recorded while participants viewed action images. EMG recordings from the flexor/extensor (proximal forearm) and pronator teres muscles (distal forearm) was acquired in order to assess coherence between the brain and the designated skeletal muscles.

Specific Aim #4

Question

Does impaired sensory feedback affect neural network patterns when identifying action goals in right-handed individuals?

Aim

Evaluate the effects of impoverished sensory feedback of the dominant limb during action understanding.

Hypothesis

Immobilization of the dominant limb will shift limb mapping strategy used for action interpretation to the non-dominant limb and therefore alter neural networks to accommodate the perturbation.

Approach

Using EEG, cortico-cortical coherence will be evaluated to determine whether immobilization of the dominant arm will effect action interpretation.

Organization of the Dissertation

This dissertation is organized into eight chapters and appendices. Chapter 2 introduces the relevant work addressing general background information and motivation for this dissertation. In Chapter 3, the methodologies used to accomplish this work are presented and justified. The following four chapters describe Aims one through four. In each chapter, the aim is restated, experimental design is described in further detail, followed by the results of the experiment and a discussion of the findings. The final

Chapter 8 includes an integration of all four aims findings and a discussion for future work.

CHAPTER 2

BACKGROUND

Motor Simulations

How we transform motor commands into actual movements is a complicated and fascinating area of study. We have the ability to learn from and communicate with others through movements. An increasing number of studies indicate that the motor system has an important role in motor simulation. Movements, whether generated by ourselves or by watching others, activate similar neural networks seen during motor simulations (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). The motor system is active for activities such as imitating and predicting the intentions of others (Fadiga, Fogassi, Gallese, & Rizzolatti, 2000). This concept follows the well-known theory that observing an action activates common neural processes via the mirror neuron system (Rizzolatti & Craighero, 2004). "Mirror neurons" were discovered when neurons recorded in area F5 in the premotor cortex of a Macaque monkey discharged when the monkey performed a particular action and also when it observed that same action being performed (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). When an individual sees an action being performed, neurons that encode that action are activated in the observers' premotor cortex. Since then, they have also been identified in the inferior parietal lobule (Fogassi et al., 2005). Activation of mirror neurons drives motor simulations without motor output and provides us with the capability to understand action performed by others from our own perspective (Jeannerod, 2001; Rizzolatti et al., 1996).

As proposed, motor simulation is an essential function of the motor system. During observational learning, children observe adults performing behaviors and learn them without being explicitly taught (Blandin, 1999). This occurs when a seen action is performed, the motor system of the observer maps the observed action onto a mental representation of their own body in order to perform the action. Motor simulation has also been shown to be temporally similar to the action being performed in real-time and has the ability to predict the outcome of action (Springer, Parkinson, & Prinz, 2013). This supports that participants engage in motor simulations of actual physical movement by utilizing motor command details such as velocity and position of the body. Additionally, Jennerod (2001) proposes that through simulating the action in oneself, the action being observed can be understood. This creates a match between the action itself and the motor system of the observer. An action is fully understood when the observer's motor system 'resonates' after seeing an action (Rizzolatti, Fogassi, & Gallese, 2001). Such a direct matching of the action provides a proposed mechanism for efficient recognition of action goals (Brass, Schmitt, Spengler, & Gergely, 2007).

Mirror Neurons and Action Observation

The ability to understand action seems to require an imitative capability that allows a person's own motor system to precisely organize body motion in order to achieve an observed movement. There is evidence that when performing goal-specific tool-use actions, there are specific brain areas that become active during the preparation and execution phases of a movement. Current neurophysiology shows that there are bilateral cortical areas that are connected in order to form the Action Observation Network: the ventral premotor cortex, inferior parietal lobe, and superior temporal sulcus (Gazzola & Keysers, 2009; Keysers, 2009) (Figure 2.1). These areas of the brain are engaged in the planning, observation and actual execution of an action (Cattaneo, Caruana, Jezzini, & Rizzolatti, 2009). In a functional magnetic resonance imaging (fMRI) study, connectivity between the frontal and parietal areas during an action observation task was shown (Molinari et al., 2013). During the task, subjects either viewed static images of a hand grasping an object or a video clip of a similar action. The results for the observation of static images showed a network that included posterior parts of the parietal lobe, dorsomedial frontal cortex, and dorsal ventral premotor cortex. Similarly, in an electroencephalography (EEG) study, cortico-cortical coherence was used to demonstrate the synchronization of parietal-frontal networks (Wheaton, Nolte, Bohlhalter, Fridman, & Hallett, 2005). They proposed a left lateralized parietal-premotor-motor network for the planning and execution of skilled movements. This study shows the functional coupling between these specific brain areas. Lesions to the parietal and premotor areas produce ideomotor apraxia which disrupts the ability to imitate hand gestures and mime tool-use (Hanna-Pladdy, Heilman, & Foundas, 2001; Heilman, Rothi, Mack, Feinberg, & Watson, 1986).

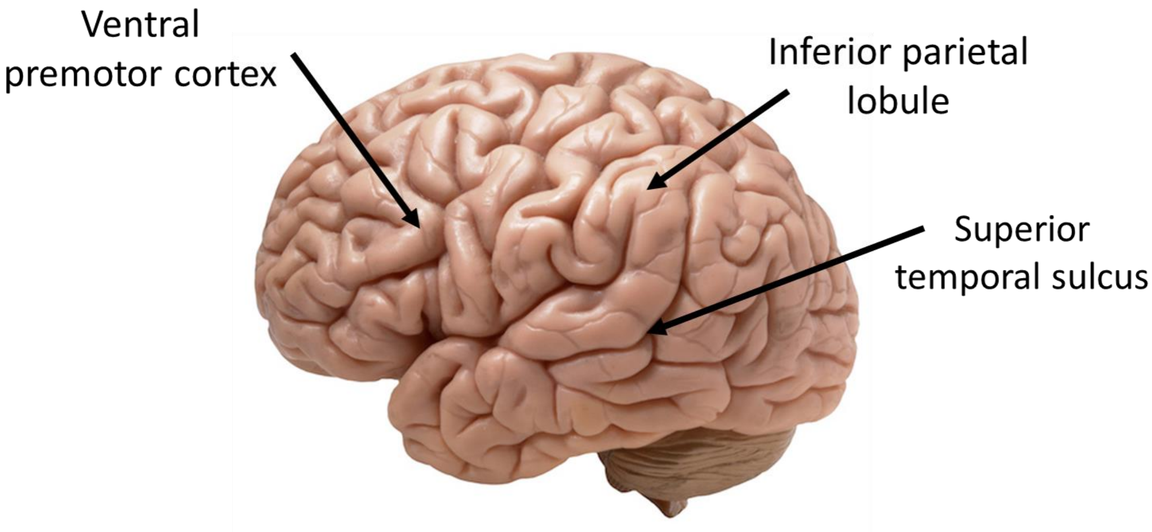


Figure 2.1: Shows the three areas that compose the action observation network. This network is composed of the ventral premotor cortex, inferior parietal lobe, and the superior temporal sulcus.

Because previous studies used right-handed subjects, for action observation, it is possible that such a left hemisphere network is selectively activated due to the selection of right-handed participants mapping seen action to their dominant (right) limb. Consequently, this would activate the left hemisphere due to participants mapping all seen actions (regardless of which limb is seen) to their dominant limb in order to interpret action. Thus, limb dominance could affect the hemisphere of action encoding. It is unknown what would happen if left-handed participants were exclusively recruited due to their exclusion from most neuroimaging studies. If all actions are mapped to the participants dominant limb, left-handed participants would have an opposite right lateralized parietal-premotor-motor network. Alternatively, it possible that regardless of which limb is seen, a left lateralized network occurs because the left hemisphere is specialized for simulating action as well as tool-use information for all subjects, regardless of hand dominance.

Predictive Coding During Action Observation

Previous studies have proposed how the left-lateralized network functions during the understanding of an action goal. First visual information generates activity in the superior temporal sulcus, which then produces activity in the inferior parietal lobe, and finally causes activity in the premotor cortex (Kilner, Friston, & Frith, 2007). However, more recent studies have suggested a dual pathway internal model for action understanding. The dual pathway model includes both a forward model and an inverse model (Kilner, 2011; Schippers, Roebroeck, Renken, Nanetti, & Keysers, 2010). The forward model (also known as the predictor) predicts the most likely outcome from the action observed. This is done through semantic retrieval and selection which allows for the most probable action to be matched to the most likely goal given the context. Here, only the goal is known to optimize motor commands. The inverse model, or controller, used concrete representations of the encoded action which works as a simulator to predict the sensory consequences of the action. This communicates the differences between the goals selected and the desired sensory output. The inverse model follows a backward pathway by focusing on the action outcome and calculating the anticipated motor command. It includes what the sensory consequences could be dependent on the most likely executed action. In order for this is occur, predicted sensory information is compared to actual sensory information from the observer (Kilner, 2011). Taken together, the predicted intention of an observed action goal is generated through a ventral pathway (forward model). Here a probable goal is selected, and then sensory consequences are generated through a dorsal pathway to make a match between the selection and outcome of the observed action. This creates a natural link between the central and peripheral systems in the observer.

Forward and inverse models complement each other during action observation and have been proposed to transform observed action into simulating the action internally to predict the outcome (Wolpert, Doya, & Kawato, 2003). The forward model changes the observed action into a predicted action goal and the inverse model generates the predicted sensory consequences of the seen action. The sensory outcome of the simulated action can be compared to the actual outcome to assess the prediction (Gazzola & Keysers, 2009; Wolpert et al., 2003). For example, when a seen action is performed with the arm, such as reaching out to grab a cup of coffee, the motor system drives internal models that predict what will occur next given the current state of the body and the motor command (Wolpert & Miall, 1996). In the forward model, visual information identifies the hand and the cup as an object, action associations are made between the cup and the hand based on experience, and finally the most probable action for reaching out to grab the cup by the handle is selected given the picture. The inverse model encodes the action to predict sensory consequences of picking up the cup and determine the best fit given the position of the body.

Action observation in several neuroimaging studies have shown the left hemisphere to be dominant for the selection of action (Iacoboni & Zaidel, 1996; Schluter, Krams, Rushworth, & Passingham, 2001; Schluter, Rushworth, Passingham, & Mills, 1998). These previous studies investigating motor resonance have mostly been done using right-handed participants observing actions with the dominant right hand. This leaves our understanding of motor dominance and action encoding limited due to left-handed actions and left-handed participants being excluded. If only right-handed participants are used in studies, this could influence the suggested left lateralization of the currently proposed action encoding network. We need to understand the physiology of the action encoding system because we would be able to clarify how motor representations are developed during action observation, how they are mapped onto the observer's motor system, and what variables can influence the lateralization of the action encoding network.

Perspective and Handedness

It is unclear how a participant's handedness and the hand involved in seen actions may affect action interpretation. In previous work using right-handed participants, it has been shown that the left cerebral hemisphere is specialized for tool use action (Frey, Funnell, Gerry, & Gazzaniga, 2005b; Raymer et al., 1999). Neuroimaging studies have shown left lateralization in right-handed participants for both left and right hand tool pantomime movements (Cabino, 2010; Choi et al., 2001; Johnson-Frey, Newman-Norlund, & Grafton, 2005; Moll et al., 2000). Recently, studies propose that each hemisphere of the brain is specialized for certain motor skills of the contralateral hand. The dominant right arm (left hemisphere) is associated with precision and specialized control during a motor task. The non-dominant left arm (right hemisphere) is associated with support and stability during a motor task (Bagesteiro & Sainburg, 2002; Sainburg, 2002). Gandrey et al (2013) suggested these two roles work together to complete a bilateral movement (Gandrey, Paizis, Karathanasis, Gueugneau, & Papaxanthis, 2013). The right arm is guided by internal forward models which simulate upcoming movements, while the left arm is reliant on feedback from the right arm to adjust support as needed in order to accomplish the task. Such a pattern could support the idea that in right-handed individuals, observing dynamic skills would always activate motor resonance within left hemisphere networks (associated with the right hand which is optimal for precision and control). Further, if right-handed individuals see actions that would promote resonance with right hemisphere networks (associated with the left hand), we would expect for behavioral deficiencies to be seen in action encoding processes. This would indicate that during action understanding it is most efficient to map an action to the dominant limb in order to interpret the most likely action outcome. As similar neural structures are engaged during action observation and execution, it is suggested that action observation creates an internal copy of that action in the observer's motor system, which can then be used to simulate the use of that object (Buccino et al., 2001). Here, it is shown that seen actions are mapped to existing motor representations to create an action-goal "match" within the observers' sensorimotor system. However, it is still unknown if both left and right hands resonate differently in the observers' motor system.

The anterior intraparietal cortex (AIP) has been shown to be active during observed and performed grasping actions of the hand. This area is sensitive to which hand is seen by the observer, the left or right hand (Biagi, Cioni, Fogassi, Guzzetta, & Tosetti, 2010). Observing grasping tasks showed increased activation when the participant viewed the actions with the contralateral hand compared to the ipsilateral hand, thus introducing a hand identity effect. This parallels the direct matching hypothesis which states that during the observation of action, the observer's motor system maps the observed movement onto their own motor system (Strafella & Paus, 2000).

One variable that has been studied is the perspective of observed actions. Mentally simulated actions from an egocentric perspective (first person) are considered visually and motorically familiar (Conson, Mazzarella, Donnarumma, & Trojano, 2012; Ni Choisdealbha, Brady, & Maguinness, 2011) as this allows optimization of motor imagery and action encoding. Alternatively, the allocentric perspective (third person) may not be motorically familiar to an observer, and in order to process allocentric action, motor imagery may necessitate visual transformations. In Ni Choisdealbha et al. (2011), they showed that right and left-handed participants were faster at judging hand stimuli in an egocentric orientation that corresponded to their own dominant hand. It was proposed that this effect was due to better utilization of visual and sensorimotor information to facilitate judgments in the dominant limb (Ni Choisdealbha et al., 2011). In allocentric orientations, behavioral strategies shifted to "visual only" so that participants could reorient the stimuli to align with 'self' as a method for interpretation. This in turn suggests that participants use a self-centered motor strategy to interpret action. However, in understanding actions in daily living we commonly view others from an allocentric perspective. Observers may use different strategies to translate, or map, actions in order to interpret the outcome based on the perspective in which the action is seen. There are two possible ways an action can be mapped to the observers' motor system in the egocentric or allocentric perspective. In the egocentric perspective, an action can be mapped to the hand that is performing the action (limb match) or the action can always map to the observers' dominant limb. In the allocentric perspective, action can be either mapped to the hand in front of them as if that observer was looking in the mirror (mirror match) or the action can be mapped directly to the observer's actual matching limb (limb match).

The process of how we generate accurate motor simulations is proposed to be reliant on the context of the movement and sensory feedback of the limb. However, the neurophysiological mechanism of how perspective and handedness interact and affect motor simulations is not yet understood.

Corticospinal Pathways

The corticospinal pathway is the most direct way the brain controls motor neurons that innervate skeletal muscles. Movement is performed by an elaborate network of hierarchical feedback loops (Kandel, 2012). The lateral corticospinal tract is the largest and controls movement of the extremities, and is responsible for goal-directed limb movements. It begins from three locations in brain: the primary motor cortex, premotor and supplementary motor areas, and the parietal lobe (Blumenfeld, 2013). Upper motor neurons extend from these areas in the cortex through the posterior limb of the internal capsule, cerebral peduncle, and into the brain stem. At the brain stem two main tracts are formed at the pyramidal decussation (Al Masri, 2011). Approximately 90% of the upper motor neurons cross over the medulla and form the lateral corticospinal tract and the remaining 10% do not cross over to form the anterior corticospinal tract. In the lateral corticospinal tract, axons travel down in the white matter columns of the lateral spinal cord. The axons continue down the spinal cord until they synapse on lower motor neurons in the anterior horn of the spinal cord. Axons from the lower motor neurons leave the spinal cord through the ventral root, join to the dorsal root to form the spinal nerve, and ultimately innervate the skeletal muscle.

According to Buccino et al. (2001) motor resonance occurs when the observation of an action drives an internal replication of that action in the observer’s motor system (Buccino et al., 2001). Some previous studies have demonstrated enhanced corticospinal pathway excitability during the observation of movement, through an increase in motor evoked potentials (MEP) amplitude of the participant’s matching muscle (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Funase, Tabira, Higashi, Liang, & Kasai, 2007).

MEPs are electrical signals recorded from either descending corticospinal pathways or from muscles after cortical stimulation of a motor area. MEPs are recorded from matching muscles from an observed action in order to detect the size of the signal. For example, when watching an index finger move, MEPs recorded from the index finger compared to MEPs recorded from any other finger will be much larger (Maeda, Kleiner-Fisman, & Pascual-Leone, 2002; Romani, Cesari, Urgesi, Facchini, & Aglioti, 2005). In a study by Baldissera et al. (2001), they tested spinal cord excitability during action observation by stimulating the H-reflex in a finger flexor muscle. The H-reflex is a refractory reaction that is recorded by EMG after stimulation from electrodes. They showed that during action observation, there was a motor-resonant mechanism at the spinal cord level that was also correlated temporally with the observed hand movement (Baldissera, Cavallari, Craighero, & Fadiga, 2001). These findings suggest that observing an action causes an increase in corticospinal activity which exactly matches the muscles involved in producing the same observed action. Additionally, this study indicates that seeing an action causes a sub-threshold activation of the task which prevents unwanted movement generation.

Being able to understand networks in the cortex, and how the cortex communicates with the periphery, is vital to understanding the neurophysiology of predictive coding of action. Understanding how hand and perspective influence corticospinal excitability and how it influences motor simulations can enrich our knowledge about the motor system in healthy subjects and can provide a framework for treating clinical populations. It is important to know which factors are most influential in motor simulation during the observation of actions because increased effectiveness of the simulation process can increase the success of the impact of motor simulation rehabilitation protocols. The goal of this dissertation was to identify the neural and neural-muscular physiology of the action encoding system and how perturbations alter motor simulations. From this we can create a more complete model for how we ultimately understand action.

CHAPTER 3

EXPERIMENTAL DESIGN

Electroencephalography (EEG)

Electroencephalography (EEG) is a noninvasive measure of electrical brain activity that has millisecond temporal resolution (Nunez, 2000). When cortical neurons in the brain are active, local dipole currents are produced. The currents are detectable at the surface of the scalp, which are recorded by EEG electrodes as voltage differences (Srinivasan R., 2007). When a neuron fires, the action potential is transmitted along the axon. The axon ends in synapses, which release neurotransmitters in the synaptic cleft where they bind to receptors on the dendrites of a post synaptic neuron. This can either cause an excitatory post synaptic potential (EPSP) or an inhibitory post synaptic potential (IPSP). If the neuron releases neurotransmitters on the post synaptic neuron and they cause a depolarization, making the membrane potential more positive, this brings the neuron close to the point where an action potential can fire. If the neurotransmitters cause a hyperpolarization, making the membrane potential more negative, this has an inhibitory effect, which makes it harder for an action potential to generate. A single neuron can have inputs from many different neurons. The signals received from them can be both excitatory and inhibitory. All of the post synaptic potentials are summed together to have a net effect on the neuron. If the combined depolarization exceeds threshold, the neuron will fire an action potential. Brain tissue and cerebrospinal fluid are conductive mediums, which induces a volume current that can be detected at the scalp surface. It takes tens of thousands of synchronously active neurons to produce a detectable signal that has to travel through the skull and scalp (Srinivasan R., 2007). Electrical activity from neurons produces dipolar currents in the form of post-synaptic potentials. Neurons that are radially asymmetric are not able to produce externally observable electric fields if the dipoles are opposite because the electrical contributions from different synapses cancel each other out due to the two opposite currents, positive and negative, occurring close to each other. Apical dendrites contribute the strongest measurable EEG signal because they are organized in parallel and are perpendicular to the surface of the scalp (Nunez & Silberstein, 2000). When activated, dipoles, which describe the direction and strength of current flow in an area, between the soma and apical dendrites are formed. Because the voltage fluctuations are summated, a large enough signal is generated and can be detected on the surface of the scalp by electrodes in the EEG cap.

There are several other methods that can be used to study brain function, including magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), or positron emission tomography (PET) to name a few. However, EEG has many advantages over its counterparts. EEG has a high temporal resolution, on the order of milliseconds, compared to fMRI, which takes much longer. However, the trade off to its superior temporal resolution is the degradation of its spatial resolution. EEG studies can be performed with participants sitting in an upright position and is more tolerant of participant movement during performance of a behavioral task. Additionally, EEG studies are non-invasive compared to PET and does not require the use of radioligands.

Synchronized activity of large numbers of neurons generates rhythmic oscillations which are linked to behavioral function. Oscillations are caused by feedback connections between neurons which create synchrony in the neural firing patterns. Neural networks work in synchrony to produce oscillations at specific frequencies which can be separated into frequency bands. For the purposes of this dissertation, Aim 2 and 4 will be focused on the μ band (8-10 Hz) and Aim 3 will be focused on the β band (15-30 Hz). In aims 2, 3, and 4 participants were fitted with a 64-channel EEG cap that was organized according to the International 10-20 system (Figure 3.1) (Niedermeyer & da Silva, 2005).

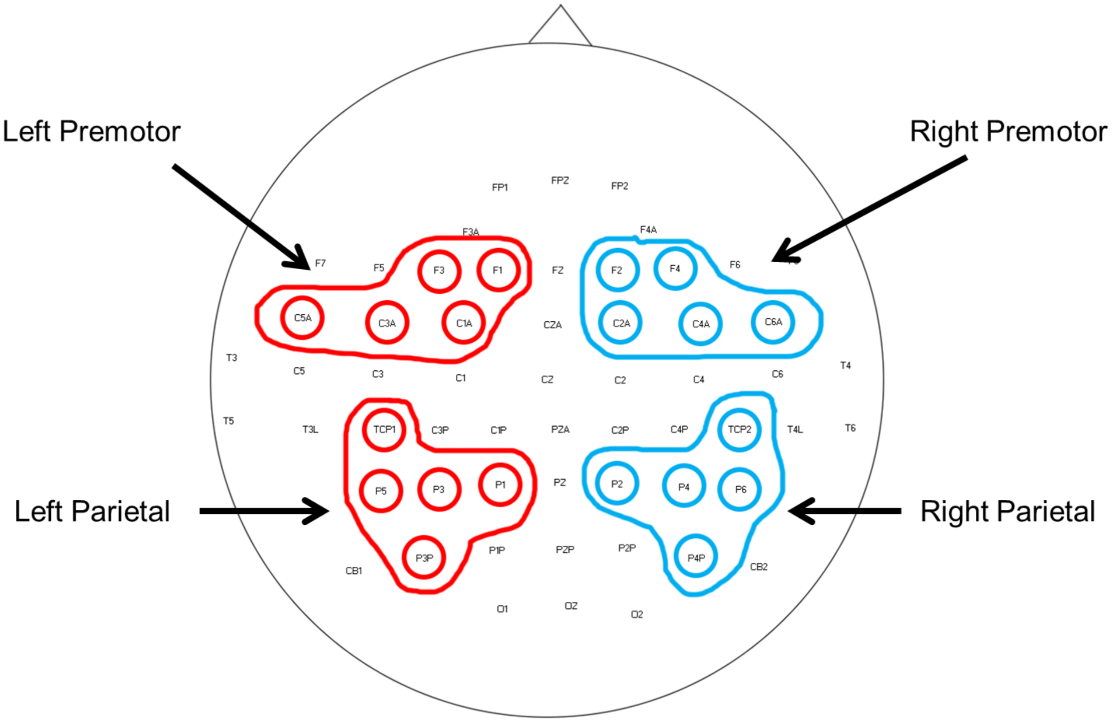


Figure 3.1: The standard International 10-20 system of electrode placement for a 64-channel EEG cap. Electrode groups of interest are highlighted and colored red (left hemisphere) and blue (right hemisphere).

The mu band was selected due to previous research stating its prevalence over areas associated with motor control (sensorimotor cortex) and because it is specifically seen during motor related tasks (McFarland, Miner, Vaughan, & Wolpaw, 2000). In early studies, the mu rhythm was discovered when it was observed to desynchronize over the sensorimotor cortex during the planning and execution of hand movement (Chatrian, Petersen, & Lazarte, 1959). Klimesch et al. (2007) proposed that information processing is higher during desynchronization ((Klimesch, Sauseng, & Hanslmayr, 2007). Depending on which hand is involved in either imagining or performing an action, the mu rhythm is prevalent in the contralateral cerebral hemisphere (Pfurtscheller & Berghold, 1989; Pfurtscheller & Neuper, 1997). Alterations in the mu rhythm during action observation have been shown to be equivalent to performing the action itself (Jeannerod & Frak, 1999; Solodkin, Hlustik, Chen, & Small, 2004). More recently it has been shown that changes in the mu rhythm amplitude occurs with visual (Pfurtscheller & Lopes da Silva, 1999) and somatosensory (Muthukumaraswamy, Johnson, & McNair, 2004) activity. Together with motor simulation alterations, this suggests the mu rhythm is involved in the understanding of action making it a natural choice for Aim 2 and 4.

The beta band is also associated with motor behavior and is seen during both the planning and execution of movement. It is observed over the sensorimotor cortex and becomes desynchronized during motor activity (Salmelin & Hari, 1994). Just like the mu band, the beta band power also decreases in the contralateral hemisphere when observing a motor task. This suggests that a change in beta power is correlated to the distribution of neural networks directly linked to the needed motor plan for the action. In Parkinson's disease, this becomes evident where a classical characteristic of the disease is difficulty or loss of the ability to initiate movement. Here, high beta activity is observed which indicates causality between the beta band and the disinhibition of needed neural networks for movement (Brown, 2007; Jenkinson & Brown, 2011). Several studies have shown that the beta band, and not the mu band, is coherent between the brain and the muscles (Kilner, Baker, Salenius, Hari, & Lemon, 2000; Mima & Hallett, 1999; van Ede & Maris, 2013). As previously described, axons from the pyramidal cells in the primary motor cortex extend down from the spinal cord to control skeletal muscles. Although the system is complex, cortico-muscular coherence has been shown to occur between the sensorimotor cortex and muscle activation. More specifically, related to this dissertation, the beta band oscillations have been shown to be coherent with EMG activity in the arm and hand muscles (Baker, Olivier, & Lemon, 1997; Conway et al., 1995; Kilner et al., 1999). Aim 3 will be focused on the beta band because it has been shown that somatosensory demands during a cued tactile identification task suppress beta band activity in both the cortex and in the muscles even in the absence of actual movement (van Ede & Maris, 2013).

Cortico-cortical Coherence

Coherence is a measure of the linear dependency of two signals at a specific frequency, which shows communication between systems or networks during a motor task (Fang et al., 2009). Imaginary coherence is a reflection of true brain interaction and is sensitive to synchronization of two processes that are phase lagged to each other in a specific frequency (Nolte et al., 2004). This method is robust as it removes the problem of overestimation biases that occur from volume conduction and other artifacts that may influence coherence. Due to the activity of a single source being able to be detected by multiple channels, imaginary coherence assumes true neural interactions must have phase lag otherwise it is considered to be artifact.

By definition, the two signals being evaluated are $x_i(t)$ and $x_j(t)$. When using EEG, the subscripts i and j represent the channels of interest in analysis. If $Z_i(w)$ and $Z_j(w)$ are complex valued Fourier transforms of both *i* and *j* channels, then by definition the cross-spectrum is:

$$B_{ij}(w) = (z_i(w)z^*_j(w))$$

The (*) indicates complex conjugation. Next coherence can be normalized cross spectrum:

$$C_{ij}(w) = B_{ij}(w)/(B_{ii}(w)B_{jj}(w))^\wedge 1/2$$

Coherence is a complex number that contains both magnitude and phase information. The measured dependency between the two designated channels is commonly evaluated. This can be assessed by taking the absolute value of $C_{ij}(w)$.

Coherence values are always between 0 (no coherence) and 1 (optimal coherence). In the case of event related paradigms, a baseline can be subtracted which shifts the coherence values between -1 and 1 indicating subsequent decreases (negative) or increases (positive) relative to baseline in the beginning of the epoch. Because coherence in this dissertation is event related, we sought to measure the dependency of coherence as a function of time relative to the stimulus.

The analysis on the imaginary part of coherence was calculated through a mathematical equation explained in detail by Nolte et al. (2004). Through this equation, the part of coherence that represents true interaction (void of volume conduction) is isolated. The equation assumes the signals in channels *i* and *j* come from a linear superposition of K independent sources $s_k(w)$ and $x_j(w)$.

$$x_i(w)=\sum a_{ik}s_k(w)$$

Because imaginary coherence assumes that the source from the electrode is instantaneous, the cross spectrum can be calculated as follows:

$$S_{ij}(f) = <x_i(w)x_j{}^*(w)> = \sum a_{ik}a_{jk}|s_k(w)|^2$$

The temporal window of coherence analysis of interest in this dissertation was based on the detailed theoretical methodology in this previous work. This work focused on the time of ~400 ms (280-526 ms, centered at 408 ms), based on prior studies showing that neural responses related to comprehension of skilled action occur within the first 400 ms of the image presentation (Mizelle & Wheaton, 2010a, 2010b). For all possible channel pairs, cortico-cortical coherence was calculated within the mu band (8-10 Hz) using a Hamming window filter and non-overlapping 256 ms time windows across the time interval of the entire epoch based on previously published methodology (Wheaton et al., 2005) relative to a 512 ms baseline before the onset of the warning cue. In Aim 2, a full electrode array of imaginary coherence was calculated, where coherence from any single channel was calculated with respect to all other channels. Statistically significant electrode pairs were plotted for comparison of spatial coherence pattern distinctions for all conditions. This methodology allows unbiased selection of significant coherent patterns in the entire electrode array that may result in overall spatial patterns of coherence for each condition. In Aim 4, electrodes were selected from regions of interest as seen in previous work (Wheaton et al., 2008) and used as a representative sample to observe laterality patterns after altering sensory feedback.

Electromyography (EMG)

EMG has been previously paired with EEG in a number of studies used to assess cortico-muscular coherence (Johnson, Wheaton, & Shinohara, 2011; Mima & Hallett, 1999; von Carlowitz-Ghori, Bayraktaroglu, Waterstraat, Curio, & Nikulin, 2015). The source of the EMG signal is the currents resulting from action potentials of active motor units during a muscle contraction. As populations of motor units are activated, the sum of the activity is detected by the electrodes and recorded (Criswell, 2010). For Aim 3, surface electromyography (EMG) electrodes recorded muscle activity from the left and right pronator teres and extensor carpi radalis longus. These muscles were chosen due to their involvement in the action seen. EMG was acquired in order to assess coherence between the brain and muscles (1000 Hz sampling rate, filtered 0-100 Hz). Additionally, participants were squeezing hand dynamometers during the experiment and live recording of the activity of the EMG electrodes demonstrated that the participants was being compliant during the experiment.

Cortico-muscular Coherence

In Aim 3, cortico-muscular coherence was used in order to determine the functional coupling between cortical areas and muscle activations. The value of understanding this is to see how cortical commands influence motor simulations. Cortico-muscular coherence is a measure of the oscillatory activity in a particular frequency band in the brain and its correlation with muscle activation. Coherence is calculated between the EEG electrodes (from the sensorimotor cortex) placed on the scalp and EMG electrodes that are placed on the designated skeletal muscle. Cortico-muscular coherence is seen in the beta band during moderate and sustained muscle contractions (Baker et al., 1997; Kilner et al., 1999; Mima, Simpkins, Oluwatimilehin, & Hallett, 1999). Therefore, squeeze of hand measurements were focused on 30% of the individual subjects' maximal voluntary contraction. Additionally, it has been shown that beta band cortico-muscular coherence can be modulated by visuo-motor tracking tasks (Perez, Lundbye-Jensen, & Nielsen, 2006). For the purpose of this dissertation, we created a static hand grip task to induce cortico-muscular coherence and then observe perturbations in the coherence values when the subjects viewed action images.

In a study by Riddle and Baker (2005), peripheral neural feedback loops from the arm were altered by cooling the forearm to a low temperature to decrease the peripheral conduction times (Riddle & Baker, 2005). Results suggested manipulation of motor outputs and afferent pathways altered cortico-muscular coherence. In Aim 4, we used immobilization to perturb the coherence pathways and observed how cortico-cortical coherence changed.

CHAPTER 4

DIFFERENTIAL MECHANISMS OF ACTION UNDERSTANDING IN LEFT AND RIGHT-HANDED PARTICIPANTS: THE ROLE OF PERSPECTIVE AND HANDEDNESS

Introduction

Understanding skilled action is a basic aspect of our daily living. Skilled action in humans frequently involves the use of tools in order to complete action goals. Previous research suggests how action understanding occurs through observation (Bekkering, Wohlschlager, & Gattis, 2000; Fadiga et al., 1995; Iacoboni et al., 1999; Rizzolatti, Fogassi, & Gallese, 2004). Action understanding likely requires an imitative capability that allows a persons' motor system to precisely organize body motion in order to achieve an observed movement. The ideomotor theory describes that action and the perception of action are related by common neural systems (Massen & Prinz, 2009). Thus perceiving another's actions or action outcomes elicits the same activation in the observer's motor system. Seeing an action and being able to recognize the possible outcomes are vital for not only the potential of motor simulation of action, but also for understanding the tool-action outcomes themselves. What remains unclear is what particular variables impact the perception of action and the understanding of action goals.

One variable that has been studied is the perspective of observed actions. Mentally simulated actions from an egocentric perspective are considered visually and motorically familiar (Conson et al., 2012; Ni Choisdealbha et al., 2011) as this affords optimization of motor imagery and action encoding. Alternatively, the allocentric perspective may not be motorically familiar to oneself, and in order to process allocentric action, motor imagery may necessitate visual transformations. In Ni Choisdealbha et al.

(2011), they showed that right and left-handed participants were faster at judging hand stimuli in an egocentric orientation that corresponded to their own dominant hand. It was proposed that this effect was due to better utilization of visual and sensorimotor information to facilitate judgments in the dominant limb. In allocentric orientations, behavioral strategies shifted to “visual only” so that participants could reorient the stimuli to align with ‘self’ as a method for interpretation. This in turn suggests that participants use a self-centered motor strategy to interpret action.

However, it is unclear how a participant’s handedness and the hand involved in seen actions may affect these results. In previous work, it has been shown that the left cerebral hemisphere is specialized for tool use action (Frey, Funnell, Gerry, & Gazzaniga, 2005a; Raymer et al., 1999). Neuroimaging studies have shown left lateralization in right-handed participants for both left and right hand tool pantomime movements (Bohlhalter et al., 2009; Cabinio et al., 2010; Choi et al., 2001; Johnson-Frey et al., 2005; Moll et al., 2000). Further, left parietofrontal lateralization for performance of tool use action was observed in left and right-handed participants using their dominant hand (Vingerhoets et al., 2012). This evidence leads to the indication that damage to the left cerebral hemisphere resulting in ideomotor apraxia (which causes the inability to correctly perform tool use and communicative gesture on command) should be a bilateral deficit (Wheaton & Hallett, 2007). Apraxia can be seen in both hands after left hemispheric damage, which suggests that the left hemisphere network controls skillful tool use knowledge for both left and right hand movements (Heath, Almeida, Roy, Black, & Westwood, 2003).

For actions seen in an egocentric (first person) perspective, limb-specific motor simulations are achievable. Under these circumstances, right-handed participants watching a right-handed action would have no dissociation of motor planning and primary motor cortex. However, due to the diminished left lateralization of motor activation of left-handed action in right-handed participants (Cabinio et al., 2010), there is the potential for some dissociation for right-handed participants watching left-handed action. This assumes that action is encoded in the participant's limb that matches the seen action. It is unclear what would happen in left-handed participants, where seeing a right-handed action may bring tool use activation and motor activation into the same hemisphere. Further, we frequently have to understand actions in daily living, and we commonly view them from an allocentric (third person) perspective. There are two possible ways an action can be encoded in the allocentric perspective in order to understand that action: limb matched and mirrored limb (Figure 4.1). Limb matched is a biological-limb match to the participant. Mirror matched would occur when watching a matched dominant limb perform an action as if you were looking in a mirror.

The motivation of this study is to evaluate how perspective and handedness interact to understand and identify tool action outcomes. Our hypothesis was that both left and right-handed participants would identify action outcomes best from an egocentric perspective. When looking at stimuli from an allocentric perspective, identification of action outcomes would best occur in mirror matched dominant limb for right and left-handed participants. This study will help us better understand how we translate handedness and motor representations from different perspectives.

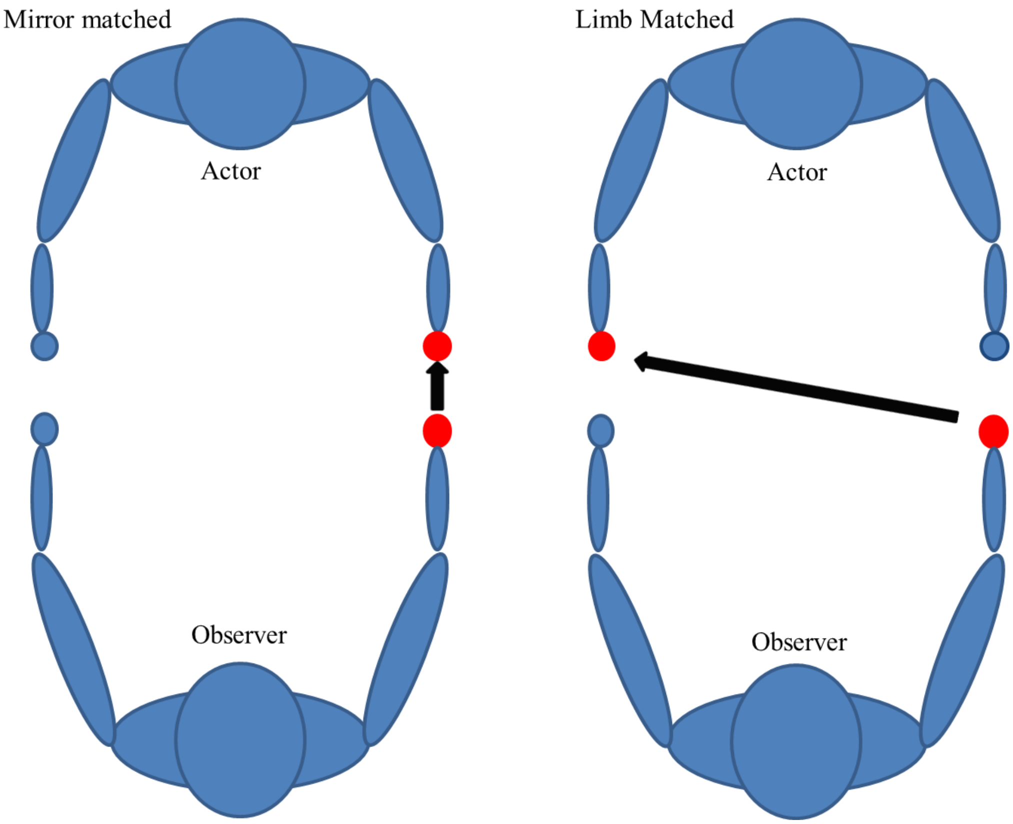


Figure 4.1: There are two possible ways an action can be encoded from an allocentric perspective: Mirror match (left) or limb-matched (right). The following figure is an example for a dominant right-handed subject.

Methods

Participants

Twenty right-handed participants (7 males; average age, 22.8, SD, 3.0) and nineteen left-handed participants (11 males; average age: 21.6, SD, 2.2) participated in the study. All participants were neurologically normal and had normal or corrected-to-normal vision. Handedness was evaluated by the Edinburgh Handedness Inventory

(Oldfield, 1971) with right-handed participants having an average score of 82.54 (SD: 15.87) and left-handed participants averaging -57.65 (SD: 26.81). If the handedness score was >+40 then the participant was right-handed and if the score was <-40 then the participant was considered left-handed. If the participant was between +40 and -40 inclusive, the participant was considered ambidextrous and was excluded from the study. The maximum score is +/- 100. The experimental procedure was approved by the Georgia Institute of Technology Institutional Review Board and consent was obtained from all participants prior to experiment.

Training

Participants were first trained on inserting and extracting tools on an upright stationary wooden board with screws protruding facing the participant. The participant had to use 3 different tools to perform the task, two were unfamiliar and one was familiar. Familiarity of the tools was confirmed verbally by participants when prompted if they knew what each tool was. If they were familiar with an ‘unfamiliar’ tool or unfamiliar with a ‘familiar’ tool they were excluded from the study. The familiar tool was a twist screwdriver, while the unfamiliar tools were a push style “Yankee” screwdriver and a rotating (plumber’s) screwdriver being used by an actor (Figure 3.2). The use of multiple screwdrivers allowed us to maintain task and instruction consistency. These screwdrivers were particularly chosen because to use them, very different actions are required, but the action outcome is the same (insert or extract a screw). The twist screwdriver uses a simple clockwise/counter-clockwise forearm rotation to insert or extract the screw. The push style screwdriver operates by pushing the driver handle that rotates the bit clockwise or counterclockwise based on the position of a toggle switch. The plumber's screwdriver is similar to the twist, except that it demands circular rotation at the wrist to insert or extract the screw. The twist is the most familiar with push and rotational being the least familiar. Of these three, the push only has one action to insert or extract the screw (the other two require clockwise or counterclockwise rotation) and it is treated as a control image. A training board was placed in front of the participant's visual field and was reachable at arm's length. Participants used each of the three screwdrivers to insert five screws all the way into the board and then reverse the same screws all the way back out to their initial starting position to obtain the motoric actions required to use each tool. Participants were instructed to choose any five screws that were at a comfortable height for them to manipulate.

Figure 4.2: A familiar twist screwdriver, a rotational (plumbers') screwdriver, and a "Yankee" push screwdriver (from left to right).

Stimuli and Task

After all training was completed, participants performed an action understanding task based on the trained tools. Participants were seated comfortably in a chair and shown randomized action images of the three different tools on a 106.7 cm (42 inch) visual monitor (visual angle = 18.7 degrees). Images were high-resolution grayscale images of either a right or left-handed instructor holding one of the previously mentioned tools in either an allocentric or egocentric perspective.

While seated with a response pad comfortably in their hands, participants were presented first with a circle (4-6 s), then a fixation cross which alerted participants that the trial was about to start (500 ms), followed by the instructor-tool image (4 s).Prior to the experiment, the participants were told the following: “The images on the screen will show you any of the tools you have just trained with, being used by either a left or right hand instructor, and can be shown either in an egocentric (as if you yourself are using the tool) or allocentric (as if you were watching me use the tool) perspective. On the image there will be a red arrow located on the wrist of the actor. Based on the direction of the arrow, you will need to simulate in your mind which way the hand is rotating, and answer if the hand is driving the screw into the board, or is it pulling the screw out of the board.” If they thought the actor was inserting the screw into the board, they were instructed to indicate by pushing the left button with their left hand on the response pad. If they thought the actor was extracting the screw, they were instructed to indicate by pushing the right button with their right hand on the response pad. Based on the stimuli presented, this afforded an equal number of responses with the left and right hands without bias to the response hand matching the stimulus hand (i.e., a correct response would equally occur for the same number of left or right hand image actions). The participant was instructed to answer as quickly and accurately as possible from the onset of the image. If the participant did not respond before the 4s time period, a fixation cross appeared and no response was counted. There were 12 different image types. Each type was displayed twice in each of the two blocks that lasted approximately 13 minutes each (Figure 4.3). All images were presented in a pseudorandom order and correctness and latency of responses were recorded.

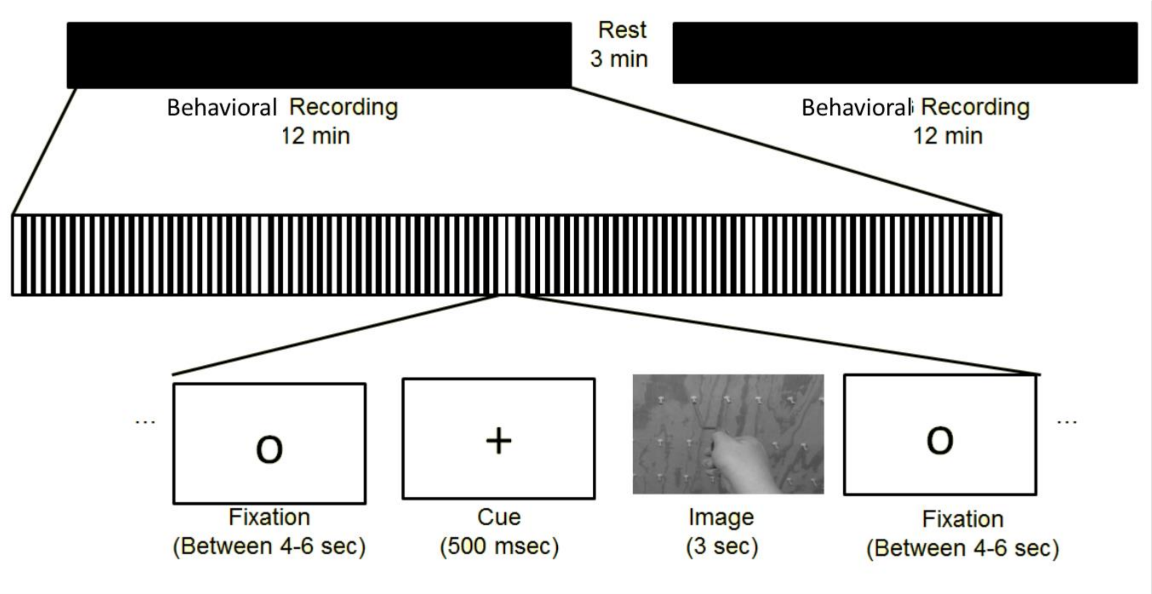


Figure 4.3: Event related illustration of the paradigm.

Analysis

Behavioral responses were recorded over two blocks of trials. All responses were recorded with Stim2 version 4.0 (Neuroscan 2003, El Paso, TX). Data was imported into Excel spreadsheets and organized by type into blocks. For each block, the response and latency average were calculated for each participant and every image type excluding any trials that the participant missed. Overall, there was no significant difference in missed trials for any image type ($p= .685$). All block averages were compiled into a grand average for each image type. Averages were then entered into IBM SPSS Statistics 19. A 4-way multivariate ANOVA (MANOVA) was computed with the following: factors perspective (egocentric and allocentric) x hand of actor (left and right hand) x tool (traditional and rotational screwdrivers) x hand of participant (left and right-handed). Where appropriate, t-tests were used to identify interaction effects between the different image types. For t-tests, significance was assessed at $p<.05$ with Bonferroni correction for all comparisons.

Results

Latency

For latency of response time, there was a main effect of perspective ($F(1, 304)= 33.66$, $p<.05$) and of tool ($F(1, 304)=9.23$, $p<.05$). In Figure 4.4 (B) it is shown that when participants look at egocentric images, they respond statistically significantly faster than if they were looking at an allocentric image. Looking at novel tool images, responses were slower when compared to familiar tools.

There were no other main or interaction effects regarding latency.

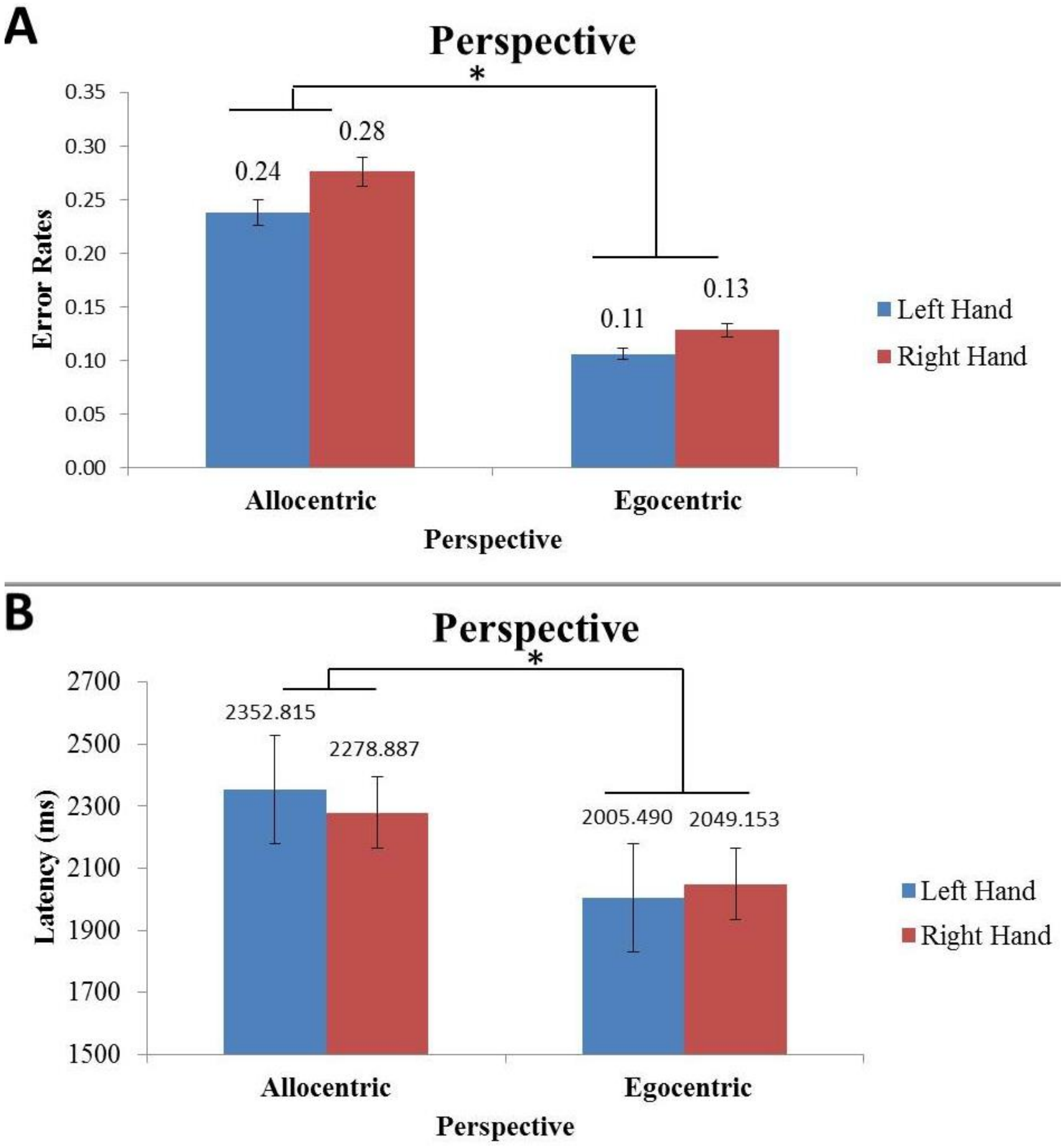


Figure 4.4: (A) shows average error rates for allocentric and egocentric images. (B) Shows the average latency for allocentric and egocentric images. The x-axis represents perspective of the image separated by hand viewed. Statistical significance is $p < 0.05$.

Accuracy

Accuracy (error rate) was also evaluated for each image type. There was a significant main effect in error rates due to perspective (*F*(1,304)=37.44, *p*<.05), with the egocentric perspective having lower error rates (Figure 4.4 A). There was a second main effect with respect to error rate for hand of participant (*F*(1,304)=8.31, *p*<.05), with right-handed participants having lower error rates than left-handed participants.

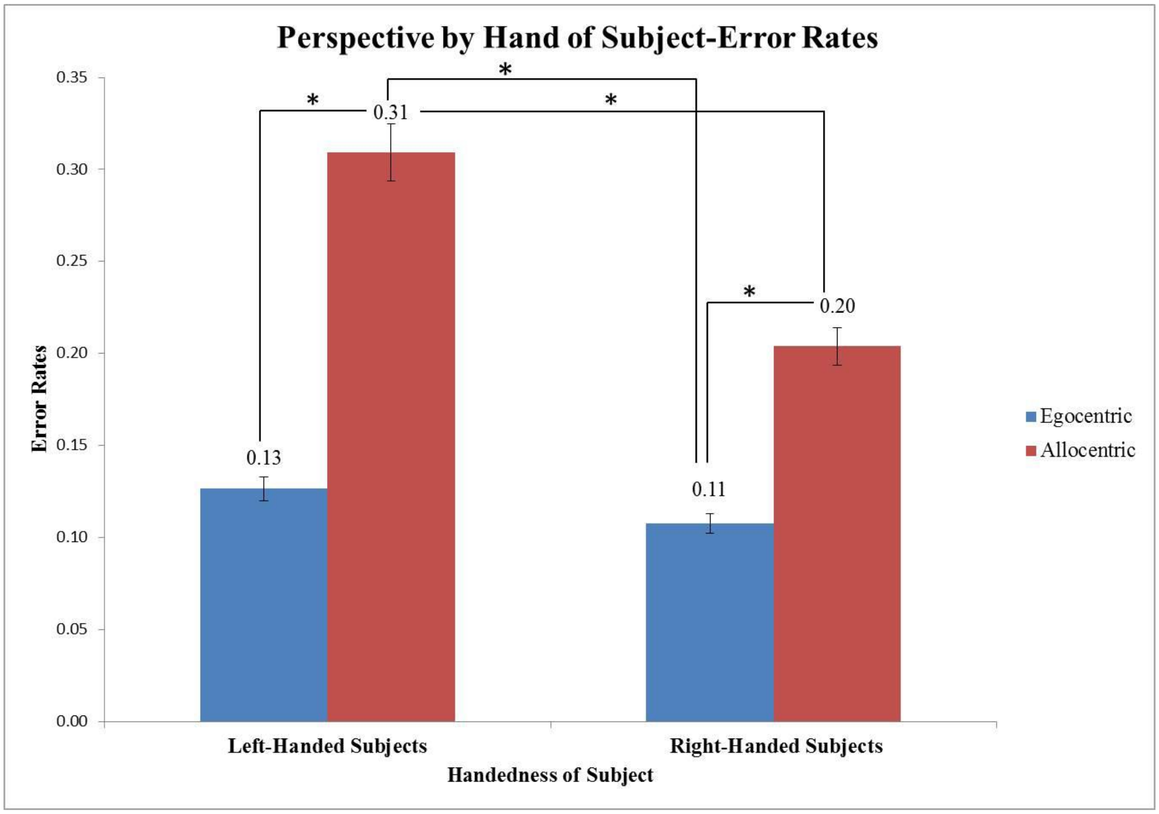


Figure 4.5: Graph shows an interaction effect between perspective and hand of subject ($p < 0.05$). Right-handed subjects looking at images in the egocentric perspective were more accurate at the task when compared to allocentric images. Overall, left-handed subjects looking at images in an allocentric perspective were significantly worse compared to all other conditions ($p < 0.05$).

An interaction effect was seen for perspective x hand of participant ($F(1, 304)=4.06$, $p<.05$). Right-handed participants looking at images in the egocentric perspective had statistically significantly lower error rates compared to allocentric images ($p=.019$). Left-handed participants looking at images in an allocentric perspective had the highest error rates overall compared to all the other conditions (Figure 4.5). An additional interaction effect was seen for tool x hand ($F(1, 304)= 4.88$, $p<.05$), however when explored, there were no individual effects.

Discussion

Right and left-handed participants were recruited in order to judge tool use action outcomes while hand of instructor, perspective, and tool type used in the images were manipulated. Specifically, we sought to evaluate how perspective and handedness interact on a learned tool in order to accurately determine an action goal using a discrete motor task. In conformation of our first hypothesis, we found that egocentric perspective images had higher accuracy and faster latencies when compared to allocentric images. Our second hypothesis was refuted, as there was no effect of handedness of participant and limb performing the action. Right-handed participants were more accurate than left-handed participants when judging allocentric images. We will further discuss our findings based on the hypotheses presented.

Allocentric versus Egocentric Perspectives

Our first hypothesis was that both left and right-handed participants would be able to judge action best from an egocentric perspective. Results revealed there was a statistically significant effect of accuracy and latency with respect to perspective for both right and left-handed participants. The highest accuracy and fastest latency were both found in the egocentric perspective for both sets of participants, which supports our first hypothesis. These findings are in line with previous studies which suggest that action outcomes are best facilitated in an internal (egocentric) perspective, regardless of the hand being used (Conson, Aromino, & Trojano, 2010; Lindgren, 2012; Oosterhof, Tipper, & Downing, 2012). Looking at previous neural studies, the left parietal lobe has been shown to be active in coding representations of the body, and the right parietal lobe is active for visuospatial orienting (Iacoboni et al., 1999; Watanabe et al., 2011). Specifically, Watanabe and colleagues (2011) studied right-handed participants who viewed and then imitated limb matched ("anatomical") and mirror matched ("specular") images performing a finger touch task. The findings in this work suggested that the more dissimilar the actors hand was from the position of the participants, the more difficulty they had in interpreting the imitation task, and there was a corresponding increase in right posterior parietal cortex (PPC) activation. They suggested that the increase in activation was due to the demands of aligning visuospatial representations with kinesthetic signals from self and therefore it was more challenging to imitate the images. These findings could explain why our behavioral results showed effects of latency and accuracy, particularly in the allocentric perspective. Together, these authors suggest that when an action is observed in the allocentric perspective, it is possible that action resonates to either of the observer's limbs as a technique to interpret action more readily. Although visual areas associated with mental rotation were not assessed, this could be a future direction to further explore the neural mechanisms driving the behavioral effect.

Effects of Handedness in Allocentric Perspective

Our second hypothesis was that in allocentric perspectives, optimal action prediction would align best in mirror matched dominant limb for right-handed and left-handed participants. Handedness of participant showed an effect on accuracy, where right-handed participants were significantly more accurate in the task than left-handed participants overall. However, neither right nor left-handed participants showed behavioral effects to the allocentric actions performed with a mirrored or matched hand, which does not support the second portion of our hypothesis. We studied action prediction by testing if the ability for resonance to occur may be impacted in a limb specific way. In action perception, according to the ideomotor theory, a participant's motor system and the associated action representations are activated when perceiving action from another person (Massen & Prinz, 2009). Perceiving body movements and corresponding remote goals influences how those actions are understood. Functional affordances include all possible tool-based goal directed actions that best "afford" a desired action goal (Mizelle, Kelly, & Wheaton, 2013). In this work, we proposed that functional affordances are critical for the ability to simulate action and understand all possible action outcomes. Importantly both body movements and action goals have a bidirectional association in order for the perception of action to trigger action in the observer (Massen & Prinz, 2009; Paulus, 2012). If the perception of action in an observer comes from bidirectional understanding of movements and goals, then mapping all seen action to the dominant or non-dominant limb in an allocentric perspective could facilitate action understanding. Although allocentric actions showed no bias to either limb for our behavioral study, Conson et al. (2010) did in fact see a limb bias in the allocentric perspective. This could be due to different experimental demands between the paradigms where our study was focused on action outcome and Conson et al. (2010) was focused on hand laterality and mental rotation. Future neurophysiological studies will further evaluate specific neural mechanisms that may relate to activation of left or right sensorimotor areas in a similar task.

When compared to right-handed participants, left-handed participants were statistically significantly less accurate when judging the outcomes of allocentric images. The decreased accuracy for left-handed participants on the allocentric images could be due to an asymmetrical lateralization of encoding action and motoric dominance in the brain, which may interfere with translating allocentric limb action outcomes within their own motor system. In prior work (Frey et al., 2005b), left and right-handed callosotomy patients were studied in order to understand hemispheric specialization for tool-use. The left-handed patient performed worse at demonstrating tool-use actions with the dominant left hand compared to their right hand, but the right-handed patient performed best with the dominant right hand and worse with the left. These results indicate that the left hemisphere is specialized for tool-use information. This idea has been well validated in human neuroimaging experiments (Vingerhoets et al., 2012). For left-handed people (because the right hemisphere controls their dominant hand), a challenge is presented when trying to access tool representations from the opposite (left) hemisphere. However, performance of tool use actions was not a disadvantage in their right-handed callosotomy patient. If tool-use information is stored in the left hemisphere for both right and left-handed people, then it is possible that because right-handed people have a dominant left motor hemisphere (creating a hemisphere match), they would have an advantage when interpreting action outcomes in our study. Extending these concepts, these results could suggest the reason left-handed participants perform statistically significantly worse in allocentric action outcome interpretation is because when they view the images they utilize an additional mechanism that is needed to facilitate coordination of information across the hemispheres. Specifically, we propose that when action is seen in the allocentric perspective, left-handed participants have an additional demand of utilizing left hemisphere action encoding along with right hemispheric motor and visuospatial rotations to comprehend action outcomes (Wantanabe et al. 2011). Importantly, right hemispheric visuospatial rotation may relate to right-handed participants performing worse on allocentric versus egocentric actions. Why this affects accuracy, but not latency is worth consideration in behavioral and neurophysiological studies to understand aspects of decision delay versus decision accuracy in similar tasks.

Effects of Latency vs. Accuracy

The finding that latency was significantly increased for allocentric images contributes to previous research that states allocentric images are harder to interpret compared to egocentric images (Ni Choisdealbha et al., 2011; Zhou, Liu, Zhang, & Zhang, 2012). However, latency effects did not persist through any other variable in this study. Given the difficulty of the task, there could possibly be no other latency differences because all images are moderately difficult, which would extend reaction time and ultimately interfere with accuracy due to the time constraints on response time. We removed the missed trials for each condition, which was 27.5% of trials in each condition (there was no significant difference in missed trials for any image type (*p*= .685), which suggests the task was equally difficult for all stimuli. Previous studies in our lab involving affordance have shown effects of action encoding in the latency domain but not in the accuracy domain (Borghi, Flumini, Natraj, & Wheaton, 2012). Whether increasing the time constraint on response interval or reducing the difficulty of action images would alter latency effects is an issue to be investigated in future research.

Alternative Explanations

There is other existing evidence that would suggest it is possible that right and left-handed participants have different strategies when it comes to interpreting action. Ni Choisdealbha and colleagues (2011) suggested that right-handed participants rely primarily on sensorimotor mental rotation. On the other hand, left-handed participants could depend initially on visual analysis and/or pictorial strategies followed by a mental rotation strategy.

Work has also been done to evaluate patients with frontal lesions on similar tasks (Chiavarino, Apperly, & Humphreys, 2007). The patients were asked to imitate mirror-matched or limb-matched stimulus. They discovered that patients had a selective deficit for imitating limb-matched responses which suggests that executive function of the frontal lobes drives the system to visually rotate the frame of reference in order for them to imitate the stimulus. They suggest that the imitation capacity was damaged for these particular patients. If this theory is true, then in our healthy population, left and right-handed participants would have had a similar deficit when judging allocentric images. Although this is a valid explanation, we believe it is unlikely due to higher order executive function, but rather differences in the motor system. A limitation of their study was that they did not separate the patients into left and right sided brain lesion groups and they also had diverse locations where the lesions were located within the frontal lobe. Apraxia in left-handed patients with left or right hemisphere damage has been evaluated in a recent study by Goldenberg (2013). He found that in left-handed patients, apraxia can occur as a result of damage to either the left or right hemisphere. Apraxia after left hemispheric damage (dissociating from manual dominance) may be explained as result of damage to the praxis relevant networks which remain in the left hemisphere. However, apraxia after right hemispheric damage could be explained as result of damage to a unique co-localization of praxis skills and spatial processing within the right hemisphere (Goldenberg, 2013). Such findings could argue for a stronger bilateral organization of praxis control in left handed compared to right handed participants.

Limitations

A limitation of the current study is that it is difficult to recruit left-handed participants that are extremely left hand dominant. Most tools are designed for right-handed people, thus left-handers acclimate and become slightly more ambidextrous for some skilled unimanual tasks. This effect could confound the interpretation of potential hemispheric dissociations, as strength of left-handedness has been shown to augment the strength of right hemispheric laterality (Cabino, 2010). Ambidextrous participants were excluded from the present study, but left-handed participants had a lower overall hand dominance score when compared to the right-handed participants on the Edinburg

Handedness Inventory scale. Each individual participant score was, according to the Edinburg Handedness Scale, beyond the ambidextrous range.

Another limitation is although we were not seeking to understand the learning of new tools, a new tool was incorporated into the study in order to obtain selection of tools that had the same action of ‘screwing.’ Our study utilized direct training for all tools presented and there was no effect of accuracy for novel versus familiar tool observed. There was an effect on latency, with novel tools overall having an increased latency compared to that of familiar tools. We did not expect to see a difference behaviorally between tool types due to previous work indicating neural networks were the same. The addition of a neural study would be able to confirm this.

Conclusion

The results of this chapter provide insight into how action-goals are encoded and interpreted by left and right-handed participants. It is demonstrated that the encoding of action for left and right-handed actors is not necessarily differentially encoded in left or right-handed participants in a way that would demonstrate behavioral differences. However, there is a benefit in the representation of actions encoded in the egocentric perspective. While the ideomotor theory can explain much of why this occurs, it is still unclear as to why left-handed participants, when viewing allocentric action, showed the pronounced deficit from other combinations of handedness and perspective. These results suggest observers may use different strategies to translate, or “map,” actions into their central sensorimotor representations in order to interpret action outcomes based on the handedness of the participant and perspective in which the action is seen. Therefore, the next chapter will further understand the physiology of motor simulation theory by determining whether hemispheric distinctions exist in cortical networks for left and right-handed individuals when anticipating outcomes of seen actions.

CHAPTER 5

DISTINCTIVE LATERALITY OF NEURAL NETWORKS SUPPORTING ACTION UNDERSTANDING IN LEFT AND RIGHT-HANDED INDIVIDUALS: AN EEG COHERENCE STUDY

Introduction

Observing an action recruits the same cortical neural structures (i.e., premotor, motor and parietal areas) as those involved in the performance of the actual execution of the action (Fadiga et al., 1995; Gallese & Goldman, 1998). Because of this, it is proposed that prediction of ongoing observed actions is also mediated by structures related to the execution of the movement by the observer (Wolpert & Flanagan, 2001).

Action simulation is the process thought to underlie how action observation is translated into action understanding. Action simulation is the ability to observe an action in another individual and re-enact that same action through mental rehearsal. Previous work has shown that action simulation can drive internal representations of actions that are temporally similar to the action being performed in real-time, thereby allowing for action prediction even if view becomes occluded (Prinz & Rapinett, 2008; Springer et al., 2013). Action simulation is driven by the parietofrontal cortical network, and is thought to give rise to our ability to understand other's intentions and action goals from a first person perspective (Rizzolatti & Sinigaglia, 2010). As similar neural structures are engaged during action observation and execution, it is suggested that action observation creates an internal copy of that action in the observer's motor system, which can then be used to simulate the use of that object (Buccino et al., 2001). Here, it is suggested that seen actions are mapped to existing motor representations to create an action-goal "match" within the observer's sensorimotor system. Current research supports the idea that the observer's motor system interacts with the parietofrontal system to encode seen actions (Peeters et al., 2009; Rizzolatti et al., 2001; Rizzolatti & Sinigaglia, 2010).

Currently, there is evidence that when performing goal-based action, specific networks are engaged during the preparation and execution phases of a movement. Using electroencephalography (EEG), physiological networks can be studied with cortico-cortical coherence (Wheaton et al., 2008; Wheaton et al., 2005). In this prior work, a strong left lateralized parietal-premotor-motor coherence was seen for the planning and execution of skilled movements in healthy right-handed persons. For action observation, it is possible that such a left hemispheric network is selectively activated due to participants mapping seen actions to the dominant (right) limb.

Although action understanding is relatively well defined, what remains unclear is how cortical representations of limb dominance (e.g., laterality of primary motor cortex) interact with parietofrontal action encoding mechanisms. Action simulation research has been primarily focused on right-handed individuals, with the hypothesis that motor resonance would engage neural processes in the right hemisphere for left-handed individuals (Goldenberg, 2013; Vingerhoets et al., 2012). Without studying left-handed individuals specifically, we cannot definitively infer that inverted right-handed mechanisms are responsible for action simulations. Left-handed individuals compose 4-16% of the population (which varies by culture (Perelle & Ehrman, 1994)), and their inclusion in motor control research is important to better understand the neurophysiology of motor systems. In doing so, we will be able to better understand how handedness can impact the neurophysiology of action understanding.

Using EEG cortico-cortical coherence focusing on the mu band (8-10 Hz), we can evaluate the temporal development of putative parietofrontal action understanding networks to determine whether they differ in left- and right-handed persons. Activity in the mu band has been observed over the sensorimotor cortex and is involved in action observation tasks (Pineda, 2005). We proposed that in an egocentric perspective, there are two possible ways a participant can map an action: to the hand that is performing the action (limb match) or always mapping to their dominant limb (dominant limb match) (Figure 5.1 A and B). In an allocentric perspective, an action can be mapped directly to the limb in front of them as if the participant were looking in a mirror (mirror match; Figure 5.1 C). Alternatively, an action can be mapped directly to the participant's actual matching limb (limb match; Figure 5.1 D). In right-handed individuals, we hypothesize based on the cortical lateralization of motor dominance, that we will see patterns of coherence that reflect a limb match strategy (cortical coherence contralateral to the seen limb). This would suggest a "limb match" mapping (as opposed to always mapping to the dominant limb) for right-handed individuals. We also expected that left-handed individuals would have a more bilateral pattern of coherence, regardless of perspective, in the parietofrontal network due to possible dissociations of tool-use knowledge and motor dominance (Goldenberg, 2013). Further, we predicted stimuli that engaged the non-dominant hemisphere would negatively affect latency and accuracy of behavioral responses.

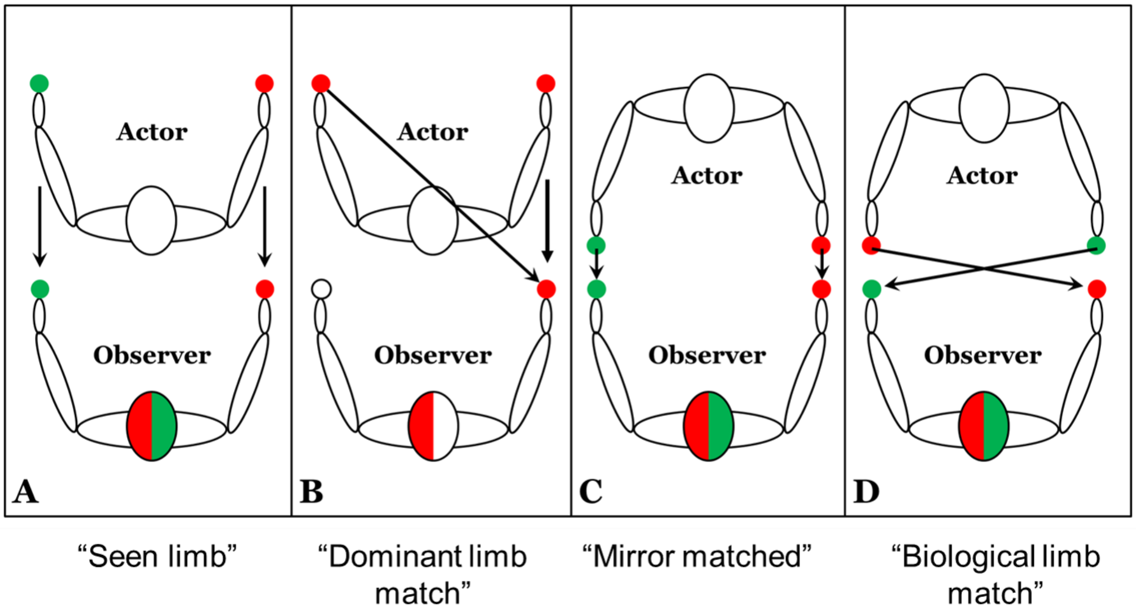


Figure 5.1: Exemplar images of possible ways action can be encoded. The matching color of the actors hand designates which hand the observer is mapping the action to and which hemisphere is consequently activated. In the egocentric perspective there are two possible ways action can be encoded: to the hand that is performing the action (seen limb match, A) or the action is always mapped to the dominant limb (dominant limb match, B). In the allocentric perspective there are two possible ways action can be encoded: as if the participant were looking in a mirror (mirror match, C) or an action can be mapped directly to the participant's limb (limb match, D). The following figure is an example for a dominant right-handed participant.

Methods

Participants

Twelve right-handed individuals (6 males; average age: 22.9, SD: 2.6) and twelve left-handed individuals (8 males; average age: 22.5, SD: 3.3) participated in the study. All participants were neurologically normal and had normal or corrected-to-normal vision. Handedness was evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). If the handedness score was >+40 then the participant was right-handed and if the score was <-40 then the participant was considered left-handed. If the participant was between +40 and -40 inclusive, the participant was considered ambidextrous and was excluded from the study. The maximum score is +/- 100. In our sample, right-handed participants had an average score of 88.37 (SD: 16.97, Range: 40-100) and left-handed participants averaged -63.79 (SD: 19.41, Range: -90 - -40). The experimental procedure was approved by the Georgia Institute of Technology Office of Research Integrity and informed consent was obtained from all participants prior to the experiment.

Training

Participants were first trained to use six different tools, three familiar and three novel (Figure 5.2), on effector objects appropriate for that tool (e.g., screwdriver-screw). A pre-experiment questionnaire was given to participants which asked them to rate from 1-5 how familiar they were with the specific tools shown (1= unfamiliar, 5= very familiar) and if they had ever used that particular tool before (yes or no answer). Those familiar with ‘novel’ tools and those who were unfamiliar with ‘familiar’ tools were excluded from the study. Familiar tools were rated and their average was 4.5 out of 5 with no participant rating any tool below 3. Unfamiliar tools were rated on average as 2.0 out of 5 with no participant rating any tool over 3. The familiar tools were a traditional screwdriver, ratchet, and a wrench. The three novel tools were a rotating screwdriver, a strap-wrench, and a flex head ratchet (secured at a 90 degree angle). These tools were particularly chosen because to use them, different actions are required to use each tool, but the action outcome is the same (to insert or extract a corresponding effector object).

Figure 5.2: (from left to right) a familiar twist screwdriver; rotational screwdriver; a traditional ratchet; a flex head ratchet; a wrench; strap wrench.

All participants were trained to use all tools in a single training session. During training with the screwdrivers, an upright stationary wooden board was placed in front of their visual field and was reachable at arm's length. Participants were instructed to choose any five screws that were at a comfortable height for them to manipulate. They were instructed to only use their dominant hand during the training session. Participants used the traditional and the rotational screwdriver (one at a time) to insert all five screws all the way into the board and then screw the same screws all the way back out to their starting position to obtain the motoric actions required to use each tool. The following task was repeated with a traditional ratchet and flex head ratchet on a board with bolts and lastly with a wrench and a strap wrench using a section of polyvinal chloride (PVC) pipe with a lid screwed onto the threading of the open end (away from the wooden board).

EEG

Participants were seated in a chair and a standard tin 58-channel EEG cap (Electrocap, Eaton, OH, USA) was fitted to their head to record neural activity (1000 Hz sampling rate) using Synamps 2 (Neuroscan, Charlotte, NC, USA). Electrooculography (EOG) activity was recorded through electrodes secured beside and below the left eye in order to capture eye blinks and movements. The EOG channels were used offline to extract eye movement artifact using autoregressive modeling (O. Bai, Vorbach, Hallett, & Floeter, 2006; O. U. Bai, Nakamura, Nagamine, Ikeda, & Shibasaki, 2001). Using Stim2 (Compumedics, Charlotte, NC), stimulus onset and behavioral responses were synchronized to the EEG time series, which allowed for the data to be epoched and analyzed.

Stimuli and Task

After all training was complete, EEG was recorded while participants performed an action understanding task based on the trained tools. Participants were seated in a chair and shown randomized action images of the six different tools on a 106.7 cm (42 inch) visual monitor (visual angle = 18.7 degrees). Images were high-resolution grayscale images of either a right or left-handed actor holding one of the previously used tools in either an allocentric or egocentric perspective (Figure 5.3). Images were controlled for size within each image type and lateral position of the arm.

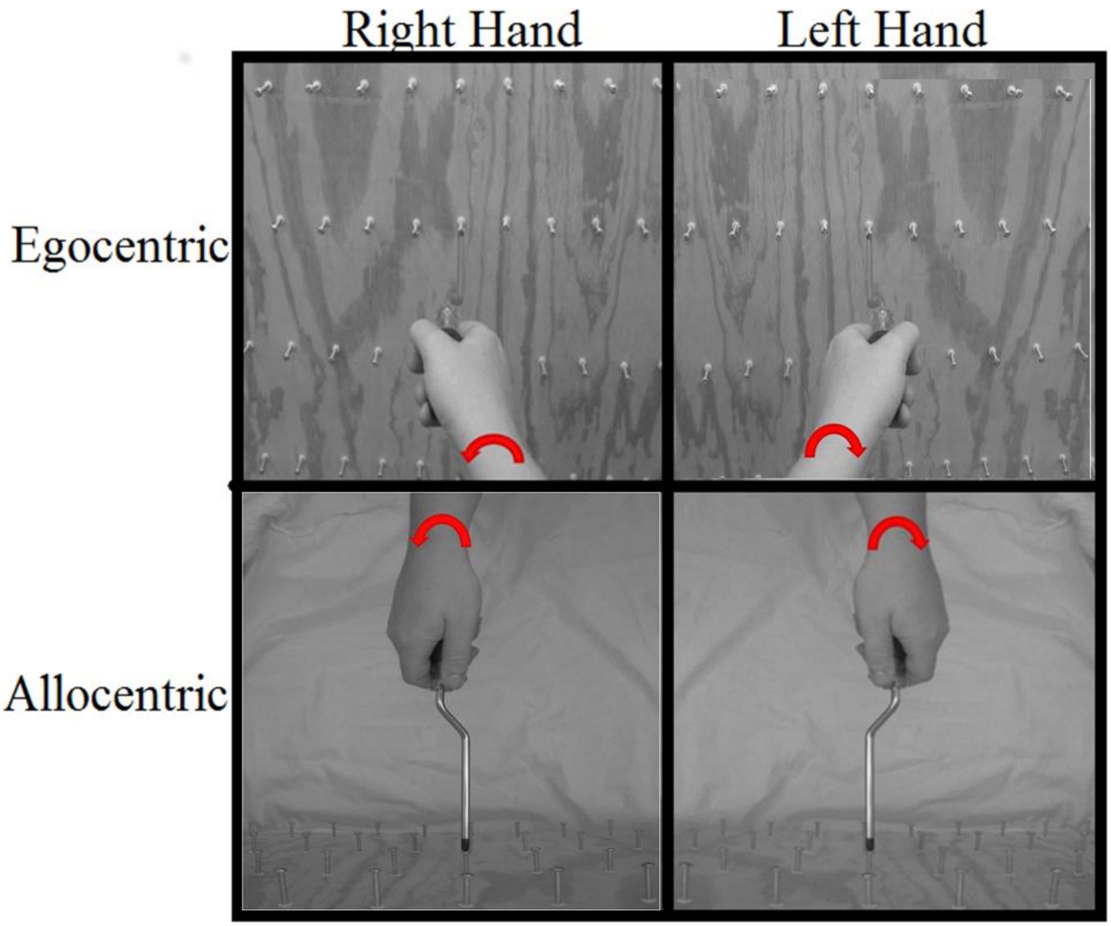


Figure 5.3: The wooden board with screws that were mounted for subject training; (upper left) a right hand in an egocentric perspective screwing a screw ‘out’ using a rotational screwdriver. (upper right) Left hand in an egocentric perspective screwing a screw ‘out’ with a rotational screwdriver. (Lower left) A right hand in an allocentric perspective screwing a screw ‘in’ with a rotational screwdriver. (lower right) A left hand in an allocentric perspective screwing a screw ‘out’ with a rotational screwdriver.

While seated with a response pad comfortably in their hands, participants were presented first with a fixation circle (4-6 s), then a cross which alerted participants that the trial was about to start (500 ms), followed by the actor-tool image (3 s). While the image was on the screen, the participants were asked to judge if the actor was inserting or extracting a screw out of the wooden board based on a red arrow located on the wrist of the actor, denoting which way the tool was being manipulated. Prior to the experiment, participants were told the following: “The images on the screen will show you any of the tools you have just trained with, being used by either a left or right hand actor, and can be shown either in an egocentric (as if you yourself are using the tool) or allocentric (as if you were watching me use the tool) perspective. On the image there will be a red arrow located on the wrist of the actor. Based on the direction of the arrow, you will need to simulate in your mind which way the hand is rotating, and answer if the hand is driving the screw into the board, or is it pulling the screw out of the board. Please do not try and perform the movement yourself.” If they thought the actor was inserting the screw into the board, they were instructed to indicate by pushing the left button with their left hand on the response pad. If they thought the actor was extracting the screw, they were instructed to indicate by pushing the right button with their right hand on the response pad. Based on the stimuli presented, this afforded an equal number of responses with the left and right hands without bias to the response hand matching the stimulus hand (i.e., a correct response would equally occur for the same number of left or right hand image actions for a given tool use image). The participant was instructed to answer as quickly and accurately as possible from the onset of the image. If the participant did not respond before the 3 s time period, the circle reappeared and no response was counted. There were 24 different image types (6 tools x 2 hands x 2 views). The experimental paradigm had four blocks that lasted approximately 12 minutes each. All images were presented in a pseudorandom order and correctness and latency of responses were recorded.

Analysis

Behavioral responses were recorded over four blocks of trials. All responses were recorded with Stim2 version 4.0 (Neuroscan 2003, El Paso, TX). Data sets were organized by type into blocks and the response and latency average were calculated for each participant and every image type excluding missed trials. A One-way ANOVA was computed for excluded missed trials in order to determine if there was a significant difference in missed trials between image types. Overall, there was no significant difference in missed trials for any image type ($p = .244$). Averages were then entered into IBM SPSS Statistics 19. A univariate repeated measures ANOVA was computed with the following within-groups factors: perspective (egocentric vs. allocentric) x hand of actor (left and right) x tool (novel and familiar), and a between-groups factor of hand of participant (left and right). Where appropriate, post-hoc t-tests were used to identify interaction effects between the different image types. For t-tests, significance was assessed at $p < .05$ with Bonferroni correction for all comparisons.

All images were presented on the monitor and a marker was recorded to indicate image onset, and subsequently used for epoching. Data were epoched 1000 ms before the onset of the image (which includes the fixation cross) until 3000 ms after onset of image (when image is turned off). Using a customized Neuroscan script, data were epoched, baseline corrected to the first 500 ms (-1000 to -500 ms), and a linear detrend was applied. The data were then sorted into the 12 conditions and a customized MATLAB (Mathworks, MA) script was used to compute the imaginary coherence for each image type. Coherence is a measure of the linear dependency of two signals at a specific frequency. Imaginary coherence is a reflection of true brain interaction and is sensitive to synchronization of two processes that are phase lagged to each other in a specific frequency (Nolte et al 2004). This method is robust as it removes the problem of overestimation biases that occur from volume conduction and other artifacts that may influence coherence. The temporal window of coherence analysis of interest was based on the detailed theoretical methodology in this previous work. This work focused on the time of ~400 ms (280-526 ms, centered at 408 ms), based on prior studies showing that neural responses related to comprehension of skilled action occur within the first 400 ms of the image presentation (Mizelle & Wheaton, 2010b). Further, prior studies have suggested that the mu band is related to action encoding properties that we are seeking to evaluate (Pfurtscheller & Neuper, 1997; Pineda, 2005). More specifically, the mu band has been shown to reflect changes in power over the sensorimotor cortex during action observation (Cochin, Barthelemy, Lejeune, Roux, & Martineau, 1998; Pineda, 2005). For all possible channel pairs, coherence was calculated within the mu band (8-10 Hz) using a Hamming window filter and non-overlapping 256 ms time windows across the time interval of the entire epoch based on previously published methodology (Wheaton et al., 2005) relative to a 512 ms baseline before the onset of the warning cue. This results in a full electrode array of imaginary coherence values, where coherence from any single channel was calculated with respect to all other channels. Pairs of electrodes showing significant coherence from all possible channel pairs were selected based on statistical threshold of all values significantly exceeding the 512 baseline values, with an alpha = 0.01. Statistically significant electrode pairs were plotted for comparison of spatial coherence pattern distinctions for all conditions. This methodology allows unbiased selection of significant coherent patterns in the entire electrode array that may result in overall spatial patterns of coherence for each condition.

Results

Behavioral Results

For latency of response time, there was a main effect of perspective (*F*(1, 176)= 9.57, *p*<.05). When participants look at egocentric images, they respond statistically significantly faster compared to allocentric images (Figure 5.4).

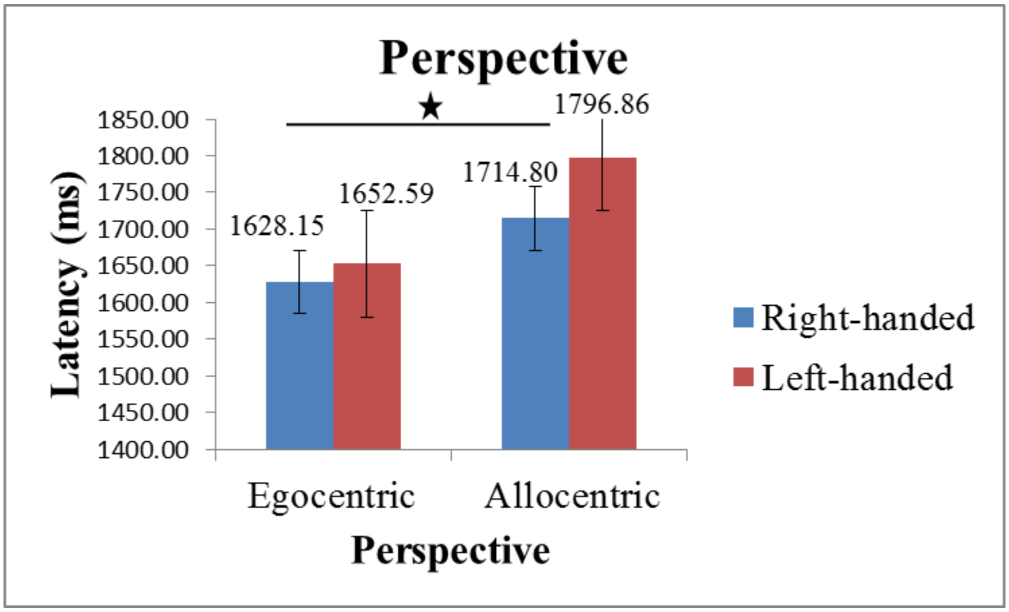


Figure 5.4: Shows average latencies for allocentric and egocentric images with egocentric images having faster latencies compared to allocentric images. Graph is statistically significant (*p*<0.05). The error bars characterize SDs.

Accuracy (percent correct) was also evaluated for each image type. There was a statistically significant main effect in percent correct due to perspective (*F*(1,176)=22.84, *p*<.05), with participants responding more accurately overall to egocentric versus allocentric images (Figure 5.5).

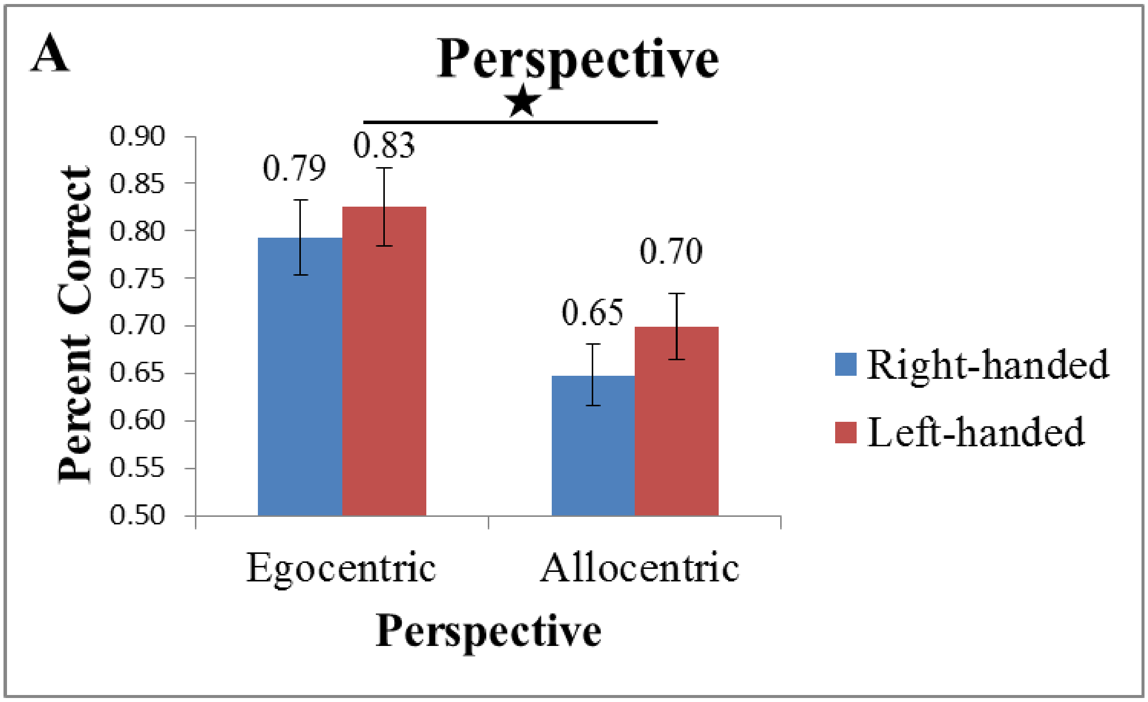


Figure 5.5: Shows average percent correct for allocentric and egocentric images with egocentric images being more accurate compared to allocentric images. Graph is statistically significant (*p*<0.05). The error bars characterize SDs.

Neural Results

There was no effect of familiarity of tool in the behavioral results, which fits the pattern of previous work suggesting that physical practice of a previously unfamiliar tool results in strong left parietofrontal activation equal to familiar tools (Mizelle, Tang, Pirouz, & Wheaton, 2011). Thus, familiar and unfamiliar tools were grouped together in the analysis of EEG data.

Figure 5.6 denotes the development of mu coherence over time for right-handed participants watching egocentric actions performed by right-handed actors. This shows that initial coherence patterns begin at ~152 ms and persist through 280-408 ms. Such a temporal pattern was common for all other conditions. This validates our *a priori* hypothesis regarding the time window of interest. Subsequent reporting will focus on the *a priori* selected time window.

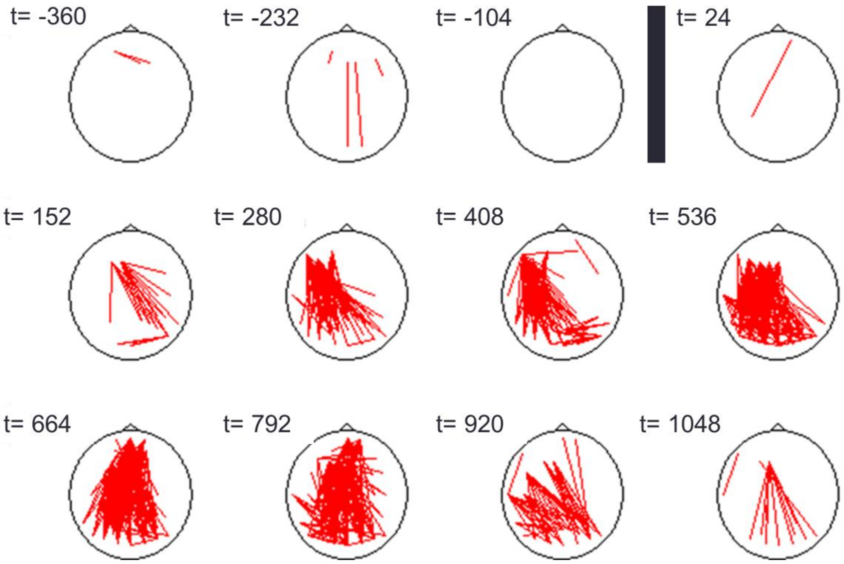


Figure 5.6: Denotes the development of mu imaginary coherence over time for right-handed participants watching egocentric actions performed by right handed participants. Black vertical line represents image onset.

Egocentric Images

For right-handed participants viewing egocentric images, statistically significant (p<0.01) coherence was seen between left hemisphere parietal-occipital and frontal areas when watching a right-handed actor (Figure 5.7 A). This would suggest that seeing a hand matching their dominant limb would map to their dominant motor hemisphere. When right-handed participants observed a left-handed actor, statistically significant (p<0.01) coherence was seen between right hemisphere parietal-occipital and frontal areas (Figure 5.7 B). This suggests that seeing a hand that matched their non-dominant limb mapped to their non-dominant left hand and therefore activated their non-dominant motor hemisphere.

For left-handed participants viewing egocentric images, regardless of which hand was seen, a bilateral pattern of coherence from parietal-occipital areas to both the left and right premotor areas was seen (p<0.01; Figure 5.7 C and D).

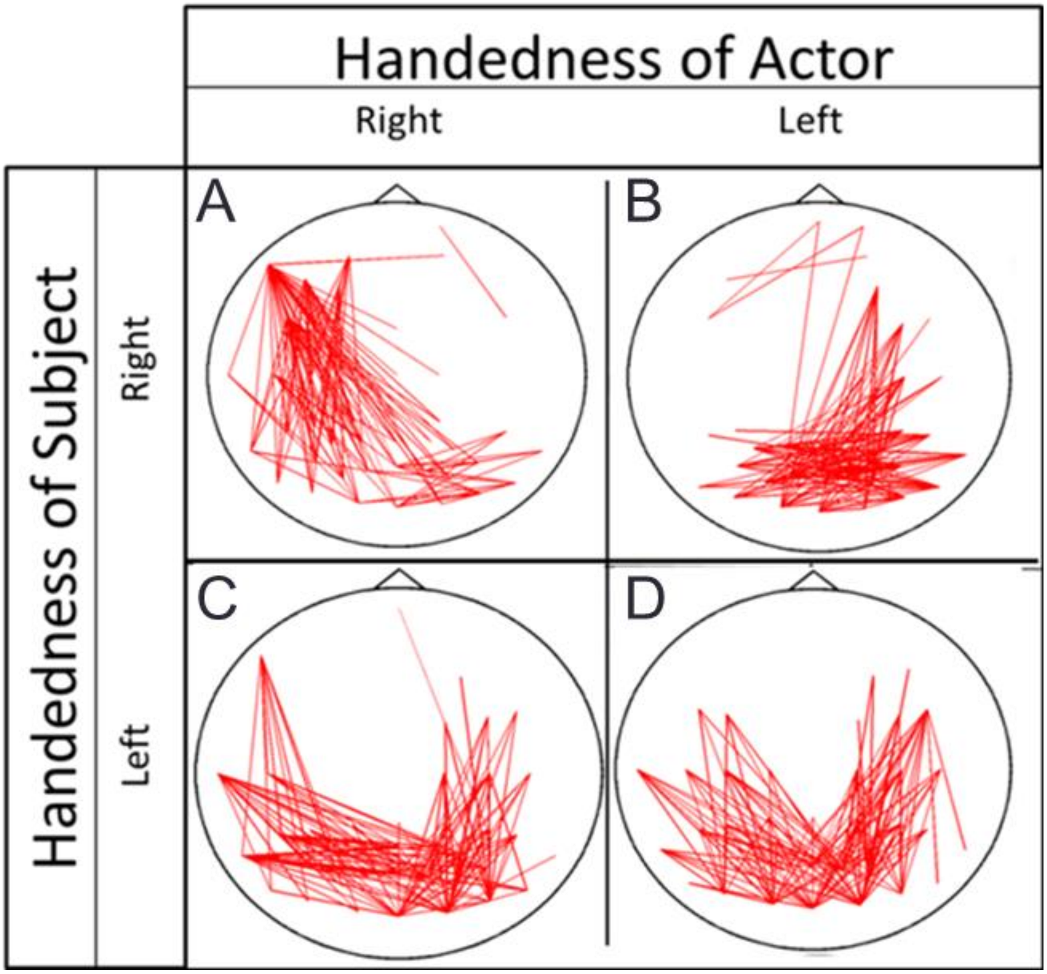


Figure 5.7: Imaginary coherence plots when subjects are viewing egocentric images. (A) Right-handed participants viewing right hands show significant coherence values between left hemisphere parietal-occipital-frontal areas. (B) Right-handed participants viewing left hands show significant coherence values between right hemisphere parietal-occipital-frontal areas. (C and D) Left-handed participants viewing right hands (C) and left hands (D) show significant bilateral coherence values between parietal-occipital areas and both left and right premotor areas. Time window was between 280-526 ms. Coherence values are significant at (p<.05).

Allocentric Images

For right-handed participants observing a right-handed actor, statistically significant ($p<0.01$) coherence was seen between right hemisphere parietal-occipital and frontal areas in the right hemisphere (Figure 5.8 A). This suggests that seeing a hand matching their non-dominant limb mapped to their non-dominant left hand and therefor activated their non-dominant (right) motor hemisphere. When right-handed participants viewing left-handed allocentric images, statistically significant ($p<0.01$) coherence was seen between left hemisphere parietal-occipital and frontal areas (Figure 5.8 B). This suggests that seeing a hand matching their dominant limb mapped to their dominant limb itself (mirror matched) and activated the contralateral (left) motor hemisphere.

For left-handed participants viewing allocentric images, regardless of the actor's handedness, a bilateral pattern of coherence between parietal-occipital areas and both left and right premotor areas was seen ($p<0.01$; Figure 5.8 C and D).

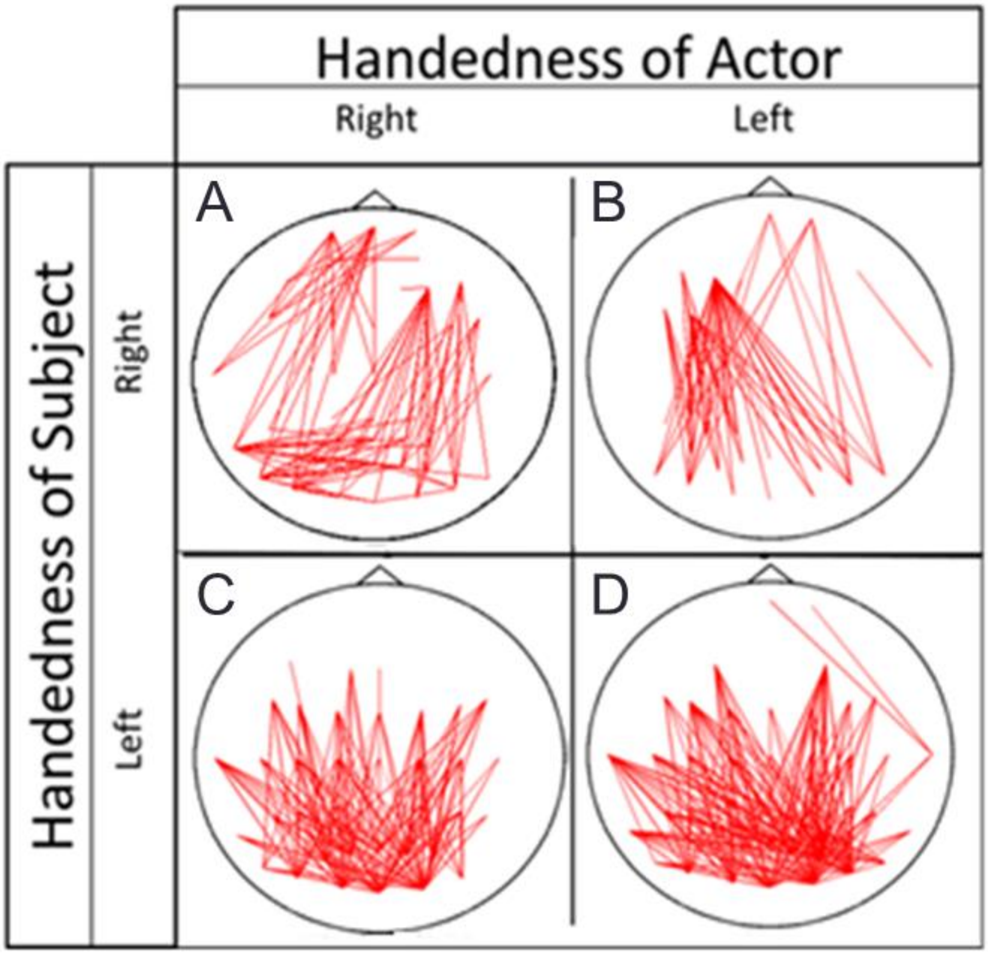


Figure 5.8: Imaginary coherence plots when subjects are viewing allocentric images. (A) Right-handed participants viewing right hands show significant coherence values between right hemisphere parietal-occipital and frontal areas. (B) Right-handed participants viewing left hands show significant coherence values between left hemisphere parietal-occipital and frontal areas. (C and D) Left-handed participants viewing right hands (C) and left hands (D) show significant bilateral coherence values between parietal-occipital areas and both left and right premotor areas. Time window was between 280-526 ms. Coherence values are significant at (*p*<.05).

Strength of left-handedness

According to the Edinburg Handedness inventory, left-handedness is defined as scoring -40 to -100. Our left-handed participants had a higher degree of variability in this range of scores (-40 to -100). Comparatively, right-handed participants generally score between 80-100. We performed an analysis of coherence on left-handed participants with a score of -80 to -100 (termed ‘extreme left-handed’ (n=5)) to see if there were any differences compared to the group of persons that we considered more weakly left-handed (-40 to -70; n=7) participants. Both groups showed similar patterns of strong bilateral parietal-occipital and frontal coherence.

Discussion

In this work, right and left-handed participants viewed images of goal-based behavior, judging tool use action outcomes while perspective, hand of actor and tool type used in the image were manipulated. We sought to evaluate, behaviorally, how perspective and handedness interact when determining an action goal from a discrete motor task. We additionally sought to determine potential interactions of perspective and handedness on the laterality of cortical coherence patterns between parietofrontal areas in right and left-handed individuals when viewing different action images. We hypothesized that in right-handed individuals, based on the cortical lateralization of motor dominance, we would see patterns of coherence that reflected a limb match strategy (cortical coherence contralateral to the limb seen). Further, we hypothesized that stimuli that resulted in neural circuits involving the non-dominant hemisphere would negatively affect latency and accuracy of behavioral responses. We also expected that left-handed participants would have bilateral coherence patterns regardless of perspective in the parietofrontal network. In confirmation of our hypotheses, we found that right-handed participants had left-lateralized parietofrontal networks when evaluating right-handed egocentric images, and when evaluating left-handed allocentric images. Correspondingly, networks involving the right parietofrontal areas were predominant when right-handed persons looked at left-handed egocentric images and right-handed allocentric images. This pattern suggests that actions viewed in an egocentric perspective use a limb match strategy to simulate action. However, in an allocentric perspective, using a 'mirror match' strategy may be a preferable way to simulate actions. Left-handed participants had a more bilateral pattern of parietofrontal coherence regardless of perspective. This supports the proposal that left-handed individuals have a less lateralized network for action understanding. We will discuss these results in the context of previous studies below.

Limb Matched Cortical Lateralization in the Egocentric Perspective

For right-handed participants looking at actions being performed with the right hand in an egocentric perspective, we observed a left lateralized coherence pattern in parietofrontal regions. This would suggest that seeing a hand matching their dominant limb would map to parietofrontal circuits aligned to their motor dominant hemisphere. Neuroimaging studies have shown that the same neural networks that are active for the execution of the action are also active when mentally simulating the action (Guillot & Collet, 2005; Jeannerod, 2001; Mizelle et al., 2013), indicating that in the egocentric perspective, participants internally simulate the observed action without any actual movement. It has been suggested that participants rotate their own hands mentally in order to interpret an action image (Parsons et al., 1995). Seeing a hand that is in an egocentric perspective matches easily with the observer and suggests action simulation is used to interpret the image. The highest response accuracy and fastest response times were found in the egocentric perspective (for both left and right-handed participants), in line with prior studies (Conson et al., 2012; Kelly & Wheaton, 2013).

Correspondingly, when the observed hand switched to the non-dominant hand (in an egocentric perspective), we observed a right-lateralized coherence pattern in the same regions with additional coherence values projecting across the occipital lobe. This would suggest that observing a hand that matched the non-dominant limb would map to the non-dominant motor hemisphere. There will be more on the unique patterns seen in right-handed participants seeing left-handed actions later in the discussion. Behavioral results correspond with this result by showing that perspective has a significant effect on accuracy and latency. When the perspective of the action image is allocentric, the opposite hemisphere drives the motor simulation indicating perspective not only has a behavioral effect, but additionally changes the way we interpret action images neurally.

Mirror Matched Cortical Lateralization in the Allocentric Perspective

For right-handed participants viewing actions performed with the right hand in an allocentric perspective, we observed a right lateralized coherence pattern in parietofrontal regions. In our previous behavioral results (Kelly & Wheaton, 2013), allocentric images showed no behavioral effects. Accordingly, we proposed these findings refuted a possible "mirror matched" hypothesis and suggested that allocentric images may map to the dominant hemisphere. When right-handed participants looked at actions being performed with the left hand in the allocentric perspective, the participants mapped the action to their dominant limb (mirror-matched). However, the present neural data suggests that seeing a right hand in the allocentric perspective caused right parietofrontal coherence (to the non-dominant limb), in keeping with the mirror matched limb proposal. Notably, there was a behavioral consequence of this strategy. For allocentric images, the observed hand is not in a congruent position and it is suggested that visual imagery is vital to interpret the action image (Brady, Maguinness, & Ni Choisdealbha, 2011; Conson et al., 2012). Utilizing different cognitive processes could explain the behavioral differences we observe here. Behavioral findings showed that participants were slower and less accurate with allocentric versus egocentric images. Thus, it is possible that mapping to the non-dominant limb affects action outcome predictions. However, as will be discussed below, there were unique coherence patterns involving the non-motor dominant hemisphere.

Additional Coherence when Observing Non-dominant Left Hands

There are two conditions, viewing left egocentric and right allocentric images, which engage the non-dominant motor hemisphere in right-handed participants. In both of these conditions, there is additional coherence present between bilateral parietal and occipital lobes (Figure 5.7 B and Figure 5.8 A). In this current study, it is possible that we observed bilateral coherence when right-handed participants use the non-motor dominant hemisphere because it best aligns in a limb-specific way. In this case, parietal action representations may be relayed to the right hemisphere for encoding by neural structures involved with left hand motor control. Thus, there is a praxis representation that can be transferred from the left to right hemisphere to perform the task. Wheaton et al. (2008) suggested that the right parietal cortex stores an incomplete set of action representations based on the emergence of right parietal coherence patterns after practice of praxis movements in patients with deficits of tool use motor knowledge (ideomotor apraxia). The patients' networks shifted to the right non-lesioned cortex, which suggests that it is possible for praxis representations to be stored in homologous areas of the right hemisphere. Prior studies suggested that motor representations that are used often can be more bilaterally represented in the parietal lobes (Rapcsak, Ochipa, Beeson, & Rubens, 1993). This creates bilateral sensorimotor representations and allows for familiar actions to engage the parietal lobe bilaterally, however the right hemisphere representation is not as strongly developed as the left hemisphere (Wheaton et al., 2008). This could propose why it is possible that we see a more bilateral network of coherence in healthy participants in conditions where they map actions to their non-dominant limb.

Another hypothesis that could explain the additional coherence pattern seen in the non-dominant left hand could be because left parietal areas are proposed to be an essential component in motor attention (Castiello & Paine, 2002; Mutha, Haaland, & Sainburg, 2013). Increases in motor attention could be due to imagining performing a task with a non-dominant limb, which is a theory that can be explored in future studies.

Bilateral Coherence Patterns Observed in Left-Handed Observers

In egocentric and allocentric perspectives, regardless of hand viewed, left-handed observers showed bilateral coherence patterns within the parietofrontal network. A bilateral coherence pattern in left-handed observers suggests that both the left hemisphere (tool-use information) and right hemisphere (motor dominant) networks were activated. Left-handed individuals are naturally more bilateral in motor control tasks (Yahagi & Kasai, 1999). This would support our behavioral findings in showing they had no behavioral advantage for either hand observed. We propose this could be due to asymmetrical lateralization of encoding action and motor dominance in the brain for left-handed individuals.

Most evidence of left-handed praxis comes from patient populations. In Frey et al. (2005), left and right-handed callosotomy patients were evaluated to determine if a left hemispheric specialization for tool-use was present in the brain. Left-handed patients performed tool-use actions better with their non-dominant right hand as compared to their dominant left hand. This suggests that left-handed patients have a left hemispheric specialization for tool-use, which is independent of their dominant motor hemisphere, and would therefore show bilateral patterns of coherence. Goldenberg (2013) observed that apraxia occurred in left-handed patients that had either right or left hemispheric damage. These clinical findings suggest left-handed patients have a strong bilateral network that can be explained as a result of motor dominance and praxis representations being separate mechanisms.

Additional studies propose that each hemisphere of the brain is specialized for certain motor skills of the contralateral hand. The dominant right arm (left hemisphere) seems associated with precision and specialized control during a motor task, while the non-dominant left arm (right hemisphere) is associated with support and stability (Bagesteiro & Sainburg, 2002; Sainburg, 2002).

However, in our study, since the arm was not involved in actual task execution, it is still possible that the non-dominant left hand could encode specialized motor control. It should be considered that our task involved spatially orienting the hand, which is included in support and stability tasks. This would indicate that during action understanding, it is most efficient to map to the limb seen, regardless of hand dominance, in order to interpret the action.

Limitations

A limitation of this chapter is that we did not record electromyography (EMG) activity from the arm muscles in order to quantitatively analyze that participants did not attempt to imitate the movement. Although participants were explicitly told not to perform the movement, and were observed by the experimenter not to move throughout the experiment, EMG would have confirmed that EEG patterns reflect action understanding and not action execution.

Another limitation of this chapter is that imaginary coherence analysis was computed within participant groups across all conditions. Imaginary coherence is calculated between all electrode pair combinations making it difficult to compare across participant groups. This allows only for an observational difference in neural networks between the participant groups. This was intentional to assess significant cortico-cortical pattern differences in an unbiased manner.

Conclusion

This chapter sought to provide insight into the neural mechanisms of action-goal understanding in right and left-handed participants. The results show differences in the hemispheric laterality of parietofrontal network-based coherence patterns in right- and left-handed individuals, and that there is a behavioral benefit of showing actions in an egocentric perspective compared to an allocentric perspective. In chapter 4 we hypothesized that in allocentric images, action interpretation would occur best with a mirror-matched dominant limb for all participants. In this chapter we can see that in the egocentric and allocentric perspective, right-handed participants seem to do this, but it is less clear with left-handed participants due to their bilateral projections. In order to disentangle the reasons we see bilateral projections in left-handed participants, the next chapter will determine if neuromuscular coherence patterns exist and how it explains differences in laterality patterns between right and left-handed individuals.

CHAPTER 6

CORTICO-MUSCULAR NETWORK DEPENDENT ON HANDEDNESS AND PERSPECTIVE DURING ACTION PREDICTION: TOWARDS A NEUROPHYSILOGICAL MODEL OF ACTION SIMULATION

Introduction

The work of Fadiga et al. (1995) was one of the first studies to show that during action observation and voluntary movements, EMG responses of the hand were the same as if the action was being performed. This suggests that during the observation of action, the observer's motor system maps the observed movement onto their own motor system (direct matching hypothesis)(Romani et al., 2005; Strafella & Paus, 2000). Matching is when the observed action is mapped onto, or translated into, an internal representation of the action and creates a match between the two within the observers' motor system. A direct match allows the observer to simulate all the possible goals of the seen action by re-enacting that same action through mental rehearsal (Rizzolatti et al., 2001).

Many studies have evaluated cortico-muscular activation of the human nervous system with cortico-muscular coherence (Boonstra, van Wijk, Praamstra, & Daffertshofer, 2009; Johnson & Shinohara, 2012; Perez, Soteropoulos, & Baker, 2012). Coherence is a measure of the correlation between two signals at a given frequency

(Nolte et al., 2004) and can show coupling between muscle motor units and the motor cortex (Mima & Hallett, 1999). It is still unclear how information is organized between muscles and motor cortex that allow interpretation of action images. Specifically, evaluating cortico-muscular coherence is valuable to disentangle the reason we observed the neural laterality patterns in our previous work. Cortico-muscular coherence is most commonly seen in the beta band (15-30 Hz) and can be evaluated using EEG to reflect the efferent drive from the primary motor cortex to the muscle (Gerloff et al., 2006). Recent research shows that during sustained isometric muscle contraction, cortico-muscular coherence can be seen between hand muscles and the contralateral motor cortex (Baker et al., 1997; Conway et al., 1995; Mima, Matsuoka, & Hallett, 2000; Omlor, Patino, Hepp-Reymond, & Kristeva, 2007).

Using EEG and EMG, we can evaluate the cortico-muscular coherence to extend work in chapter 5 and determine if a neuromuscular strategy exists for motor simulations and action understanding. To do this, a dual task was created, which allowed for the simultaneous performance of a motor task while performing an action prediction task, which should perturb task related cortico-muscular coherence based on the limb involved in the motor simulation. This concept was adopted from a study done by Johnson (Johnson et al., 2011), which demonstrated during a steady state unilateral motor task, there was an increase in cortico-muscular coherence between the active muscle and the contralateral motor cortex. With the addition of a non-motor task (mental math), they observed a decrease in beta band cortico-muscular coherence suggesting there is a division of attention away from the motor task. Furthermore, there was no change in force output of the muscle, suggesting that effects were occurring in the musculature.

Results from another study showed there was an increase in motor evoked potentials (MEPs) in the dominant hand of both left and right-handed participants when observing action movements. This suggests that the participants translated the action seen onto the matching limb which influenced motor resonance (Sartori, Begliomini, Panozzo, Garolla, & Castiello, 2014). Although Johnson et al. (2011) studied a unimanual task, other studies have shown contralateral cortical-muscular coherence occurs in bimanual tasks (Boonstra et al., 2009; Kilner et al., 2003), however the influence of performing a dual motor- motor simulation tasks on cortico-muscular coherence has not yet been studied.

The purpose of this chapter was to further understand the physiology of motor simulation theory by determining whether there is a matching cortico-muscular lateralization that corresponds with the cortico-cortical laterality patterns observed when viewing action images. We proposed that in an egocentric perspective, a participant will map the action to the hand that is performing the action (limb match). In an allocentric perspective, the action will be mapped as if the participant were looking in a mirror (mirror match). We additionally expect that there will be an decrease in cortico-muscular coherence corresponding to the hand the participant is mapping to. Specifically, in an egocentric perspective there will be a cortico-muscular coherence decrease from the C4 (right motor) electrode to left arm muscles when viewing a left hand and a decrease from C3 (left motor) to the right arm muscles when viewing a right hand. In the allocentric perspective patterns of decreased cortico-muscular coherence will follow a mirror-matched strategy. Here, there will be a cortico-muscular coherence decrease from the C4 (right motor) electrode to left arm muscles when viewing a right hand and a decrease from C3 (left motor) to the right arm muscles when viewing a left hand.

Methods

Participants

Twelve right-handed individuals (5 males; average age, 21.6, SD, 3.5) and twelve left-handed individuals (6 males; average age: 24.0, SD, 3.6) participated in the study. All participants were neurologically normal and had normal or corrected-to-normal vision. Handedness was evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). If the handedness score was >+40 then the participant was right-handed and if the score was <-40 then the participant was considered left-handed. If the participant was between +40 and -40 inclusive, the participant was considered ambidextrous and was excluded from the study. The maximum score is +/- 100. In our population, right-handed participants had an average score of 84.17 (SD: 11.65) and left-handed participants averaged -71.0 (SD: 23.53). The experimental procedure was approved by the Georgia Institute of Technology Institutional Review Board and informed consent was obtained from all participants prior to experiment.

Training

Participants were first trained to use five different tools on their traditional effector objects to ensure proper understanding of the visual task (e.g., screwdriver-screw). These tools were particularly chosen because to use them, very different actions are required, but the action outcome is the same (to insert or extract a corresponding effector object). Details of the training paradigm used to train each participant can be found in Chapter 5 (Kelly & Wheaton, 2013).

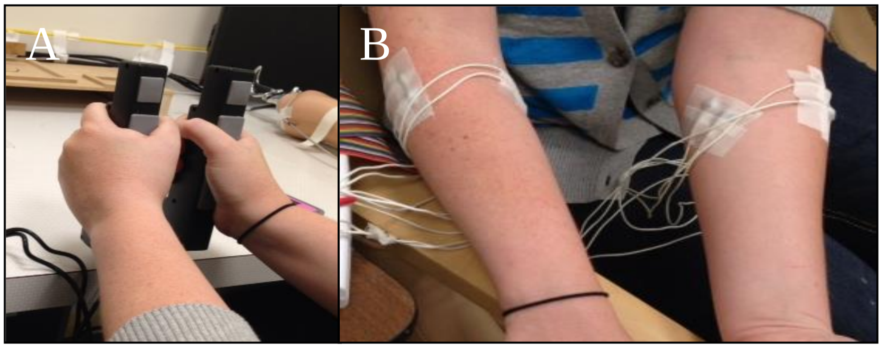


Figure 6.1: (A) Two S216 hand dynamometers. (B) EMG electrodes recording from the flexor/extensor (upper forearm) and pronator teres (bottom forearm) muscles.

Hand dynamometers are utilized to evaluate grip strength which can provide information about the upper limbs. Grip strength is highly reproducible and easy to perform (Kowanko, Knapp, Pownall, & Swannell, 1982). If arm muscles are activated, then it would be easier to observe a disruption in cortico-muscular coherence due to a visual stimulus that may evoke the cortico-muscular coherence of the limb. Consequently, two S216 hand dynamometers (Figure 6.1 A) were used to determine maximal grip strength for which 30 percent of the max was maintained during the image presentation of the experiment. The participants positioned their right and left hands around the dynamometers with their elbows at a 90 degree angle adjacent to their body with approximately a two inch separation between the elbow and the abdomen. In order to determine their maximal grip, participants completed three trials of squeezing for three seconds with maximum force. Participants were verbally encouraged to achieve maximum force and hold it for the time duration. There was a rest period of 45 seconds between each maximum squeeze. For each hand, the maximal force value was calculated and 30 percent of that force became their target. These values were calculated for both hands and averaged together. This allowed a standardized level of motor output, which was used to evaluate changes in muscle activation relative to the stimuli in each participant. Three training sessions were utilized to permit the participant to become comfortable with reliably reaching their target with no visual feedback (Figure 6.2). The training sessions were utilized to ensure participant could reach the target force output consistently during the experimentation.

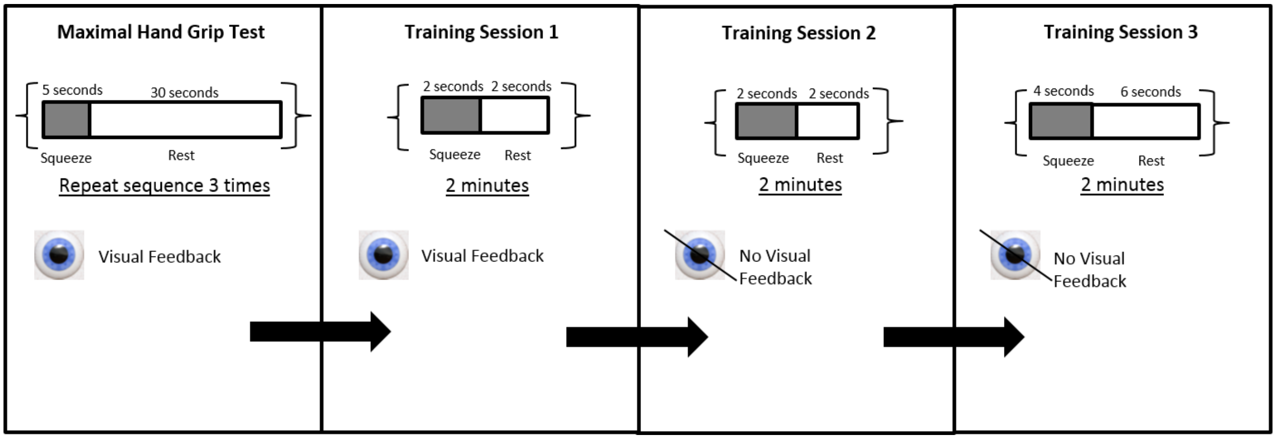


Figure 6.2: Hand dynamometer training paradigm.

Experiment

Participants were seated in a chair and fitted with a standard tin 58-channel EEG cap (Electrocap, Eaton, OH, USA) to record neural activity (1000 Hz sampling rate) using Synamps 2 (Compumedics Neuroscan, Charlotte, NC, USA). Electrooculography (EOG) activity was recorded through electrodes secured beside and below the left eye in order to capture eye blinks and movements. The EOG channels were used offline to extract eye movement artifact using autoregressive modeling (O. U. Bai et al., 2001). Using Stim2 (Compumedics, Charlotte, NC), stimuli onset and behavioral responses were synchronized to the EEG traces which allowed for the data to be epoched and analyzed. Surface electromyography (EMG) recordings from the flexor/extensor (upper forearm) and pronator teres (bottom forearm) muscles (Figure 6.1 B) were acquired in order to assess coherence between the brain and muscles (1000 Hz sampling rate, filtered 0-100 Hz).

Participants were seated in a chair and shown randomized action images of the six different tools on a 106.7 cm (42 inch) visual monitor (visual angle = 18.7 degrees). Images were high-resolution grayscale images of either a right or left-handed actor holding one of the previously used tools in either an allocentric or egocentric perspective. Participants rested their feet on an incline plane with a response pad positioned to the top of it. Participants secured their hands on the dynamometers and were instructed to squeeze them during designated times during the experiment. Participants were presented first with a fixation circle (4-6 s), then a cross which alerted participants to begin squeezing the dynamometers (1000 ms), followed by the actor-tool image (3 s). While the image was on the screen, the participant was asked to judge if the actor was inserting or extracting a screw out of the wooden board based on a red arrow located on the wrist of the actor, denoting which way the tool was being manipulated. Prior to the experiment, participants were told the following: “The images on the screen will show you any of the tools you have just trained with, being used by either a left or right hand actor, and can be shown either in an egocentric (as if you yourself are using the tool) or allocentric (as if you were watching me use the tool) perspective. On the image there will be a red arrow located on the wrist of the actor. Based on the direction of the arrow, you will need to simulate in your mind which way the hand is rotating, and answer if the hand is driving the screw into the board, or is it pulling the screw out of the board.” If they thought the actor was inserting the screw into the board, they were instructed to indicate by pushing the left button with their left foot on the response pad. If they thought the actor was extracting the screw, they were instructed to indicate by pushing the right button with their right foot on the response pad. At the onset of the fixation cross, participants were instructed to begin squeezing to their trained target level of force output and to squeeze until the picture went off the screen. The participant was instructed to answer as quickly and accurately as possible from the onset of the image. If the participant did not respond before the 3s time period, the circle reappeared and no response was counted. There were 20 different image types. Each type was displayed four times in two blocks that lasted approximately 13 minutes each (Figure 6.3). All images were presented in a pseudorandom order and correctness and latency of responses were recorded.

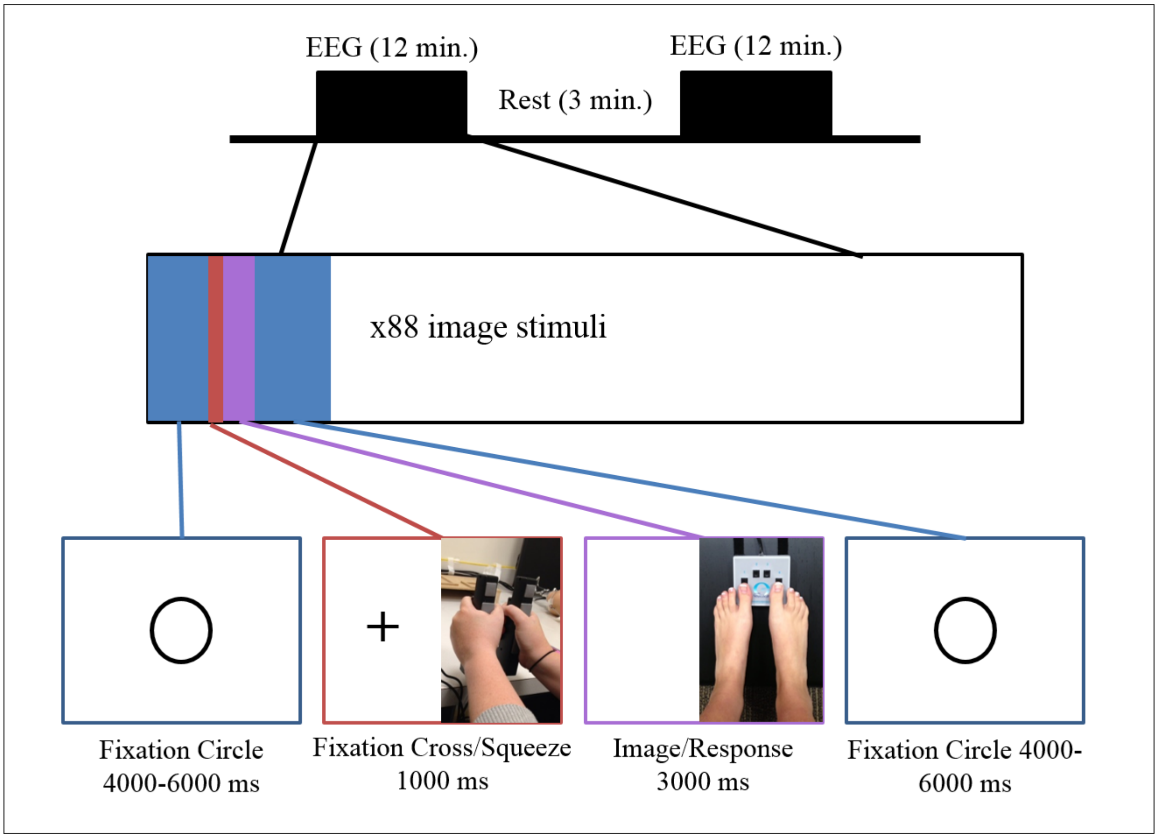


Figure 6.3: Depicts the event-related experimental design of the paradigm.

Analysis

Behavioral responses were recorded over two blocks of trials. Data sets were imported into Excel spreadsheets and organized by type into blocks. For each block, the response and latency average were calculated for each participant and each image type excluding missed trials. Averages were then entered into IBM SPSS Statistics 21. A one-way ANOVA was computed for excluded missed trials in order to determine if there was a statistically significant difference in missed trials between image types. Overall, there was no significant difference in missed trials for any image type (p = .167). A Univariate Repeated Measures ANOVA was computed with factors perspective (egocentric and allocentric) x hand of actor (left and right) x tool (novel and familiar) and a between factor of hand of participant (left and right). Where appropriate, t-tests were used to identify interaction effects between the different image types. For t-tests, significance was assessed at $p < .05$ with Bonferroni correction for all comparisons.

Hand dynamometer data were epoched, sorted, and normalized to the maximum peak within each hand for all participants. This was done to reveal if there was proportional change in force that coincided with a change in cortico-muscular coherence. A Univariate Repeated Measures ANOVA was computed with factors perspective (egocentric and allocentric) x hand of actor (left and right) and a between factor of hand of participant (left and right) to determine if there was a difference in force between any condition. Significance was assessed at $p<.05$.

For EEG and EMG data, all images were presented on the monitor and a marker was recorded to indicate image onset, and subsequently used for epoching. Data were epoched 1500 ms before the onset of the image (500ms before the fixation cross) until 3000 ms after onset of image (when image is turned off). Using a customized Neuroscan script, data were epoched, baseline corrected to -1500 to -1000ms before image onset, and a linear detrend was applied. The data was then sorted into conditions and a customized MATLAB (Mathworks, MA) script was used to compute coherence between C3 and C4 electrodes to left and right arm muscles between 15-30Hz. Coherence is a measure of the linear dependency of two signals (EMG and EEG activity) at a specific frequency. Imaginary coherence reflects true brain interaction and is sensitive to synchronization of two processes that are phase lagged to each other in a specific frequency (Nolte et al., 2004). This method removes the problem of overestimation biases that occurs from volume conduction and other artifacts that may influence measures of coherence. All cortico-muscular coherence values were computed from the C3 or C4 electrode to the contralateral flexor forearm muscle. To determine if there was a significant difference in coherence values between each hand, t-tests were performed and statistical significance was assessed at the 95% confidence interval. Statistically significant cortico-muscular coherence was observed only at 256 ms post image onset for egocentric and 512 ms post image onset for allocentric images; therefore only data from these periods were included in the analysis. All coherence values were calculated for each of the twelve subjects, normalized to the squeeze time period before the onset of the image, and averaged together across subjects.

Results

Behavioral

Latency

For latency of response time, there was a main effect of perspective ($F(1, 11)= 29.99$, $p<.05$). When participants evaluated egocentric images, they respond statistically significantly faster compared to allocentric images.

There were no other main or interaction effects regarding latency.

Accuracy

Accuracy (percent correct) was also evaluated for each image type. There was a statistically significant main effect in percent correct due to perspective ($F(1,11)=25.97$, $p<.05$), with participants responding more accurately overall to egocentric versus allocentric images. There was additionally a 3-way effect of perspective, hand and hand of participant (*F*(1,12)=6.23, *p*<.05).

There were no other main or interaction effects regarding accuracy.

Hand Dynamometer

Variability and accuracy of hand motor output were assessed for discrepancy between hands, image type, and between subject groups. Results from the hand dynamometers showed no differences in force output between right or left hands within each subject group (*p*=.778), between image type within subject groups (*p*=.982) or between right and left-handed participants (*p*=.564) (Figure 6.4). Participants executed a consistent amount of force throughout the action image regardless of picture type shown, which suggests that a change in cortico-muscular coherence to an observed action image is not likely due to differences in force output between hands or image conditions.

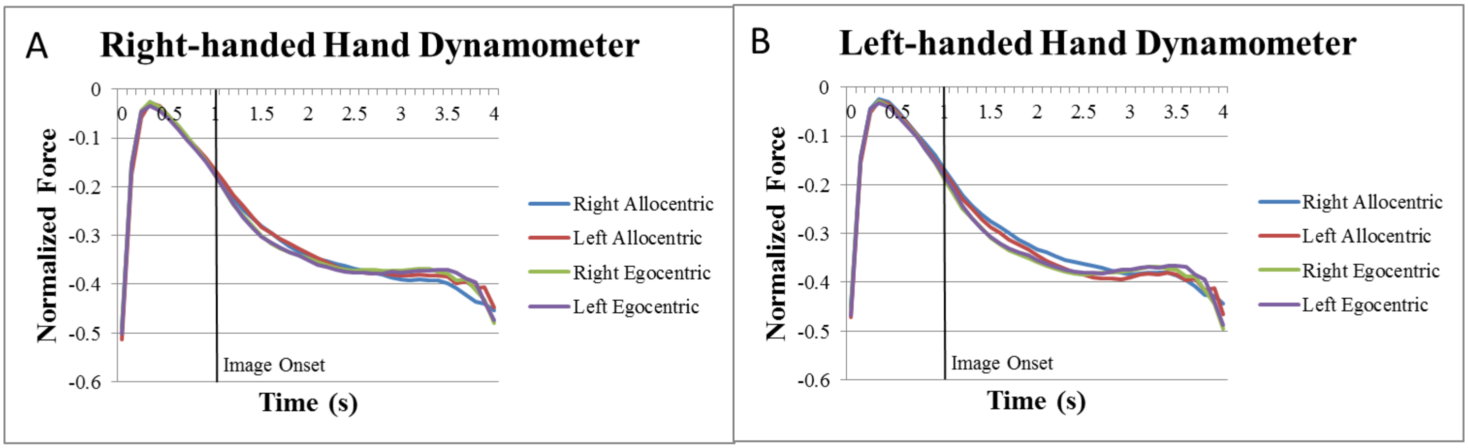


Figure 6.4: Graphs show the (A) normalized force output for the right-hand and (B) normalized force output for the left hand.

Cortico-muscular Coherence

Baseline to Squeeze

Baseline was determined to be 500ms before onset of squeeze. Squeeze was determined to be 1000ms before the onset of the image. For each individual condition, in both subject groups, baseline cortico-muscular coherence values were compared to squeeze cortico-muscular coherence values. There was a statistically significant increase for every condition from baseline to squeeze (p=.05). Figure 6.5 shows the average values for left and right-handed baseline between hands (p=.879, p=.065 respectively), left and right-handed squeeze between hands (p=.126, p=.111), and for the average of both subject groups baseline to squeeze (p=.005).

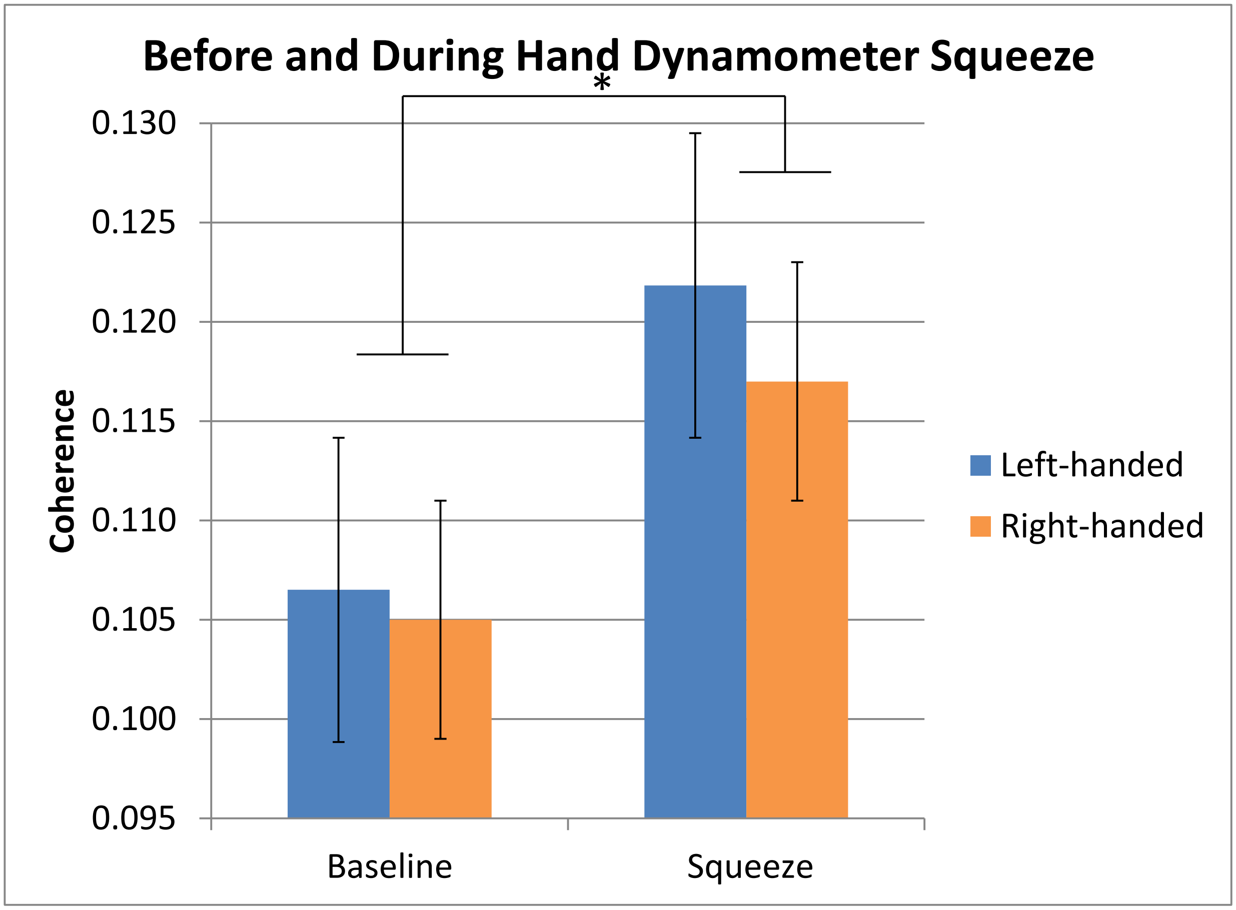


Figure 6.5: Graph shows average cortico-muscular coherence values between baseline and squeeze time bins. There was a statistically significant increase for every condition from baseline to squeeze (*p*=.05).

Right-handed Participants

To determine action understanding strategies cortico-muscular coherence was calculated and normalized to the beginning of the squeeze. To establish if there was a difference in cortico-muscular coherence between the subjects hands, t-tests were performed at each time interval from onset of image to average behavioral response time for the condition. For images that included a right-handed actor in the egocentric perspective, there was a statistically significant decrease in normalized cortico-muscular coherence to the right hand of the participant (*p*=.032) (Figure 6.6 a). For images that included a left-handed actor in the egocentric perspective, there was a statistically significant decrease in normalized cortico-muscular coherence to the left hand of the participant (*p*=.006) (Figure 6.6 b). For images that included a left-handed actor in the allocentric perspective, there was a statistically significant decrease in normalized cortico-muscular coherence to the right hand of the participant (*p*=.049) (Figure 6.6 c). For images that included a right-handed actor in the allocentric perspective, there was a statistically significant decrease in normalized cortico-muscular coherence to the left hand of the participant (*p*=.043) (Figure 6.6 d).

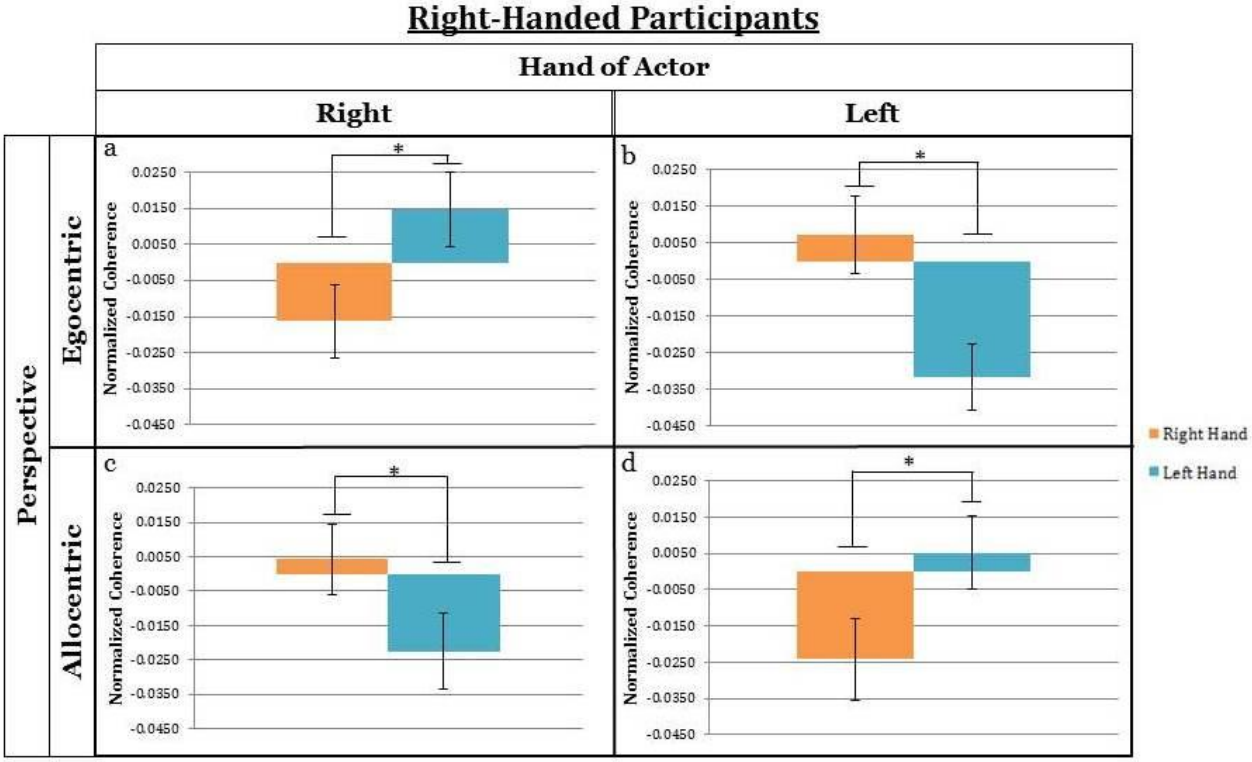


Figure 6.6: Graph shows differences in normalized coherence values between both hands for right-handed participants. In the egocentric perspective, coherence was significantly lower for the right hand when looking at a right hand image (a). When looking at a left hand image in the egocentric perspective, coherence was significantly lower for the left hand (b). In the allocentric perspective, coherence was significantly lower for the left hand when looking at a right hand image (c), and was lower for the right hand when looking at a left hand image (d). Values are significant at (*p*<.05).

Left-handed Participants

Cortico-muscular coherence was calculated the same way for left-handed participants. Much similar to when right-handed participant's mapped action on to their right hands, left-handed participants did also. For images showing a right-hand in the egocentric perspective, there was a statistically significant decrease in normalized cortico-muscular coherence to the right hand of the participant (p=.045) (Figure 6.7a). For images showing a left-hand in the allocentric perspective, there was a significant decrease in normalized cortico-muscular coherence to the right hand of the participant (p=.048) (Figure 6.7 c).

However, in conditions looking at left hands in the egocentric perspective and right hands in the allocentric perspective where participants should have mapped to the left hand, there was no significant difference (p<.05) (Figure 6.7 b and d).

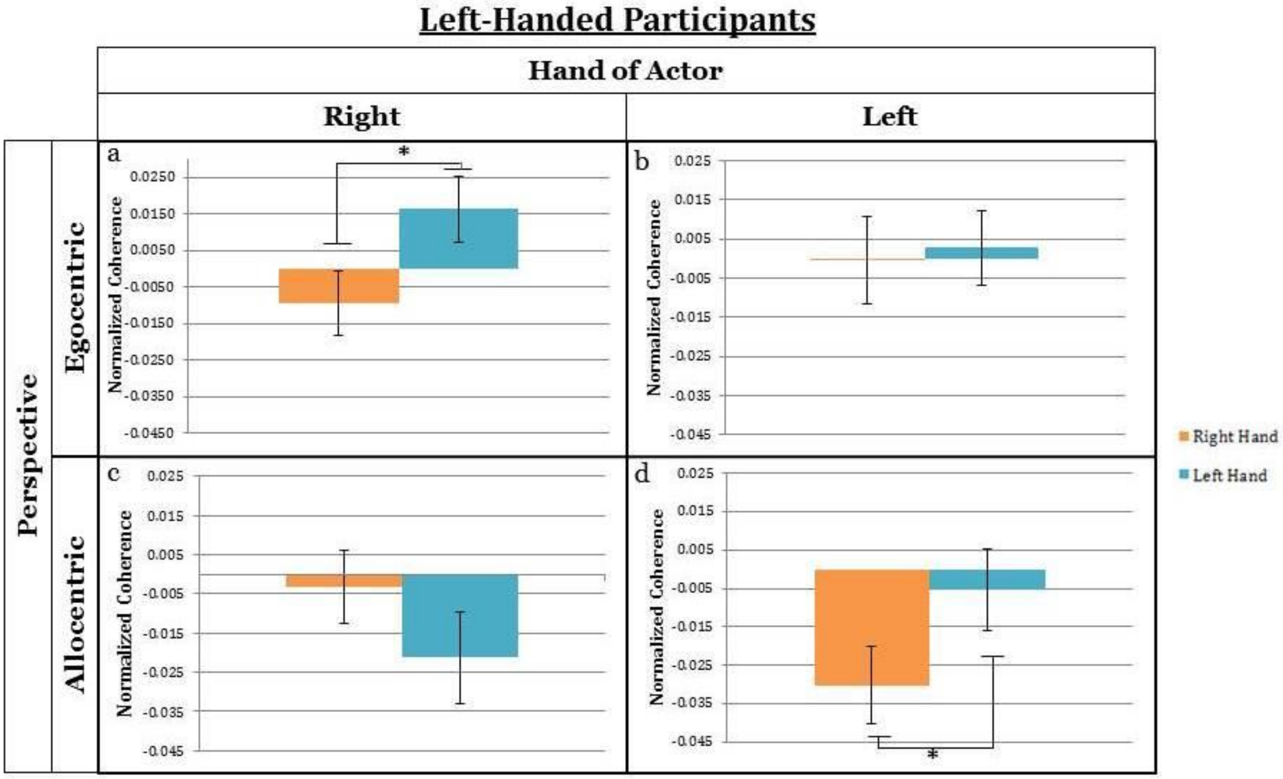


Figure 6.7: Graph shows differences in normalized coherence values between both hands for left-handed participants. In the egocentric perspective, coherence was significantly lower for the right hand when looking at a right hand image (a). When looking at a left hand image in the egocentric perspective, coherence was not significantly different for either hand (b). In the allocentric perspective, coherence was not significantly different for the left hand when looking at a right hand image (c), but was significantly lower for the right hand when looking at a left hand image (d). Values are significant at (*p*<.05).

Discussion

The main finding in this chapter, which supports our hypothesis, was that in right-handed subjects, beta band cortico-muscular coherence decreased to the hand the participant was mapping the action to, respective of perspective and handedness of the actor. These results correspond with the cortico-cortical coherence pattern seen in right-handed subjects in Chapter 5. However, in left-handed subjects, results are not as clear. In conditions where they mapped actions onto their right hand, a decrease in cortico-muscular coherence was seen. Conversely, for conditions where they should have mapped actions onto their dominant left hand, no significant different was seen.

Another important finding in this study was cortico-muscular coherence was not associated with motor output variability. Because we observed a consistent force output between both hands, this indicates that something is occurring in the musculature of the specific arm dependent on the action image seen and not on any force modulation of the hands. Previous research has suggested that seen actions elicit the same activation in the observers motor system (Massen & Prinz, 2009) but those actions are not executed (Jeannerod, 2001). This could explain why a decrease in cortico-muscular coherence in particular hands is observed. If subject is performing a steady state bilateral force modulation task, the addition of a non-motor task (interpreting action outcomes) can divide attention away from the motor task. While this would not have any effect on the force output being produced by the hands, the divided attention away from the primary task could briefly disrupt cortico-muscular coherence corresponding to hand needed for mental simulation in the additional non-motor task. Since cortico-muscular coherence was disrupted, this would suggest there is something occurring between the communication of the brain and muscle itself that correlates to the neural patterns observed in Chapter 5.

Previous studies showed there was an increase in motor evoked potentials (MEPs) in the dominant hand of both left and right-handed participants when observing actions. This suggests that the participants translated the action seen onto the matching limb which influenced motor resonance (Sartori et al., 2014). Although this study saw an increase in MEPs, it can still be implied that the decrease observed in communication between the brain and the muscle can be due to a disruption in communication. A recent study showed a decrease in beta band oscillations when performing a bimanual task during steady state contraction of the hand muscles (Johnson et al., 2011). This study suggests that the divided attention from the primary task can influence beta band cortico-muscular coherence.

What still remains unclear is why this phenomenon is only observed clearly in right-handed participants. One hypothesis is due to the bilateral cortico-cortical activity observed in Chapter 5, it is more difficult to see a significant decrease in cortico-muscular coherence. While the effects were not statistically significant, the right hand seen in an allocentric perspective showed a decrease relative to squeeze. While this is not statistically significantly different, it follows a similar trend towards the right-handed subjects.

An alternative hypothesis is that left-handed participants use a completely different network for motor simulations involving their dominant left hand. As opposed to using the motor area associated with the hand seen, they use potentially both motor areas equally. This would mitigate any effects that could be seen with a dual task paradigm because both would be modulated equally. This is not likely because we do observe some statistically significant decreases to the right hand which would suggest some motor hemisphere specificity.

Conclusion

This chapter sought to provide insight into the neuromuscular mechanisms of action-goal understanding in right and left-handed participants. The results show differences in the cortico-muscular network-based coherence patterns for right handed participants. The decrease in cortico-muscular coherence correlates to the limb seen in action images further suggesting the subjects map the action image onto their body schema dependent on perspective and hand seen. Results are less clear for left-handed individuals, which could be due to the involvement of both motor hemispheres during motor simulations.

In Chapter 4, we hypothesized that in egocentric and allocentric images, action interpretation would occur best with a limb-matched and mirror-matched dominant limb respectively for all participants. In Chapter 5, we observed that in the egocentric and allocentric perspectives, right-handed participants seem to do this, but it is less clear with left-handed participants due to their bilateral projections. The purpose of this chapter was to further understand the physiology of motor simulation theory and we determined there is a matching cortico-muscular pattern that corresponds with the previous cortico-cortical laterality patterns observed.

Recent studies have suggested a dual pathway internal model for action understanding: a forward model and an inverse model (Kilner, 2011; Schippers et al., 2010). The previous chapters have been primarily focused on the forward model. In the next chapter, we will address the inverse model which includes what the sensory consequences of an action could be dependent on the most likely possibility to the observer. In order for an accurate prediction of an action goal, predicted sensory information is compared to actual sensory information from the observer (Kilner, 2011). In the next chapter we will evaluate the role of limb sensation to better evaluate the role of sensory feedback and its role in motor simulation.

CHAPTER 7

EFFECTS OF IMPOVERISHING SENSORY FEEDBACK ON THE ACTION OBSERVATION NETWORK DURING ACTION PREDICTION

Introduction

Orthotics and braces are commonly used after a person has suffered an injury or accident to temporarily stabilize hand movements. However, studies have shown that even brief periods of immobilization can induce cortical reorganization in the brain (Bassolino, Bove, Jacono, Fadiga, & Pozzo, 2012; Toussaint & Meugnot, 2013; Wittenberg & Schaechter, 2009), particularly in the primary motor areas and somatosensory cortex (Hamzei, Liepert, Dettmers, Weiller, & Rijntjes, 2006). Short-term limb immobilization is a technique used to explore the plasticity of sensorimotor representations by decreasing the information transmitted in between the sensorimotor system. Studies have shown a decrease in excitability in the sensorimotor cortex seen as soon as several hours up to months after the immobilization of the dominant arm (Avanzino, Bassolino, Pozzo, & Bove, 2011; Lissek et al., 2009). Other evidence shows that after 24 hours of left limb immobilization, performance on a hand mental rotation task had a task repetition benefit for the right hand, but not the left. These results suggest that in healthy subjects, motor simulations are dependent on updated internal limb representations (Meugnot, Almecija, & Toussaint, 2014).

Short-term immobilization has been shown to induce sensorimotor deprivation which reduced the excitability of cortico-spinal projections (Huber, 2006; Ngomo, 2012).

In a recent study, it was shown that short-term immobilization reduces the amount of efferent muscle activation and proprioceptive sensory afferent input from the immobilized muscles (Rosenkranz, Seibel, Kacar, & Rothwell, 2014). In addition, after four days of motor restriction to selected fingers, there was a decrease in cortical excitability but the excitability of muscle, nerve, and spinal motor neurons were unaffected (Facchini, 2002). Because a large number of studies use healthy populations to study the effects of limb immobilization, their proprioception is normal and it is has been suggested that any cortical changes observed could be due to differences in proprioceptive memory of internal limb models (Moisello et al., 2008). Immobilization has also been well documented to cause cortico-motor depression which can be seen as a decrease of excitability in motor areas (Huber, 2006; Langer, Hanggi, Muller, Simmen, & Jancke, 2012).

Investigators have also shown that when mentally simulating actions, fatigue of the arm muscles significantly affected action simulation (Demougeot & Papaxanthis, 2011). Fatigue lengthened action durations when the participant was either performing the action or mentally simulating the action. They suggested that it took longer for the time to complete mental simulations to return to baseline due to the lack of updated state of limb sensory information. This occurred in the affected arm, but not the unfatigued contralateral arm. However, the validity of paradigms studying the length of time a simulated action occurs in has been debated. Overall this study showed the interdependence of sensory and cognitive systems and strongly suggests that motor simulations are heavily reliant on the current state of the participant’s motor system (Demougeot & Papaxanthis, 2011). Van Ede and Maris (2013) further supports this idea suggesting that action and somatosensation should not be thought of as two separate processes, but rather a large scale beta modulated coherent network. The somatosensory and motor cortices are mutually dependent and touch perception is an essential aspect of the network, even when no movement is performed.

Additional studies have suggested a dual pathway internal model for action understanding: a forward model and an inverse model (Kilner 2011; Shippers & Keysers, 2010). The inverse model follows a backward pathway by focusing on the action outcome and estimating the needed motor command. It includes what the sensory consequences could be depending on the most likely executed action. In order for an accurate prediction of the action goal, predicted sensory information is compared to actual sensory information from the observer (Kilner 2011). Forward and inverse models complement each other during action observation and have been proposed to transform observed action into simulating the action internally to predict the outcome (Wolpert et al., 2003). It is not yet understood how the ability to understand action or produce motor simulations is effected when sensory information is impaired.

According to Jeannerod (2001), mentally simulating an action involves sensory expectations about how a limb will move during an action. The future sensorimotor state is important to understand during mental simulation (Lorey et al., 2009). When sensory information is not compatible with the motor simulation, as in the case of immobilization, a decrease in activation in the parietal cortex can reduce the motor simulation facilitation of action interpretation (Dominey, Decety, Broussolle, Chazot, & Jeannerod, 1995).

This aim seeks to evaluate the role of limb immobilization on the neurobehavioral outcomes demonstrated in chapters 4-6 to better evaluate the role of sensory feedback on motor simulation. Specifically we aim to understand if manipulating sensory feedback of the dominant limb of right-handed participants can influence the cortical laterality patterns and behavioral responses during action interpretation. The goal is to understand the effect of sensory feedback on direct limb matching. Our hypothesis is that immobilization of the dominant limb will shift the limb mapping strategy used for action interpretation to the non-dominant limb and therefore alter neural networks to accommodate the perturbation.

Methods

Participants

Twelve right-handed participants (5 males; average age, 23.6, SD, 5.0) participated in the study. All participants were neurologically normal and had normal or corrected-to-normal vision. Handedness was evaluated by the Edinburgh Handedness Inventory (Oldfield 1971) with right-handed participants having an average score of 80.0 (SD: 10.20). If the handedness score was >+40 then the participant was right-handed and if the score was <-40 then the participant was considered left-handed. If the participant was between +40 and -40 inclusive, the participant was considered ambidextrous and was excluded from the study. The maximum score is +/- 100. The experimental procedure was approved by the Georgia Institute of Technology Institutional Review Board and consent was obtained from all participants prior to the experiment.

Training

Participants were first trained on inserting and extracting tools on an upright stationary wooden board with screws protruding facing the participant. The participant had to use 4 different tools to perform the task, twist screwdriver, push style “Yankee” screwdriver, a turnkey and a rotating (plumber’s) screwdriver. The use of multiple screwdrivers allowed us to maintain task and instruction consistency. These screwdrivers were particularly chosen because to use them, very different actions are required, but the action outcome is the same (insert or extract). Of these four, the push only has one action to insert or extract the screw (the other three require clockwise or counterclockwise rotation) and it is treated as a control image. A training board was placed in front of the participant’s visual field and was reachable at arm’s length. Participants used each of the four screwdrivers to insert five screws all the way into the board and then screw the same screws all the way back out to their initial starting position to obtain the motoric actions required to use each tool. Participants were instructed to choose any five screws that were at a comfortable height for them to manipulate.

The final training section included 2 additional tools: a traditional ratchet on a board with bolts and a wrench using a section of polyvinal chloride (PVC) pipe with a lid screwed onto the threading of the open end (away from the wooden board). Participants used each of tools to insert five items all the way into the board and then reverse the same items all the way back out to their initial starting position to become familiar with the motoric actions required to use each tool.

Stimuli and Experiment

After all training was completed, participants performed an action understanding task based on the trained tools. Participants were first seated comfortably in a chair, and fitted with a with a standard tin 58-channel EEG cap (Electrocap, Eaton, OH, USA) to record neural activity (1000 Hz sampling rate) using Synamps 2 (Compumedics Neuroscan, Charlotte, NC, USA). Electrooculography (EOG) activity was recorded by electrodes secured beside and below the left eye in order to capture eye blinks and movements. The EOG channels were used offline to extract eye movement artifact using autoregressive modeling (O. Bai 2006, and 2001). Using Stim2 (Compumedics, Charlotte, NC), stimuli onset and behavioral responses were synchronized to the EEG traces which allowed for the data to be epoched and analyzed. During recording, participants were shown randomized action images of the three different tools on a 106.7 cm (42 inch) visual monitor (visual angle = 18.7 degrees). Images were high-resolution grayscale images of either a right or left-handed instructor holding one of the previously mentioned tools in either an allocentric or egocentric perspective.

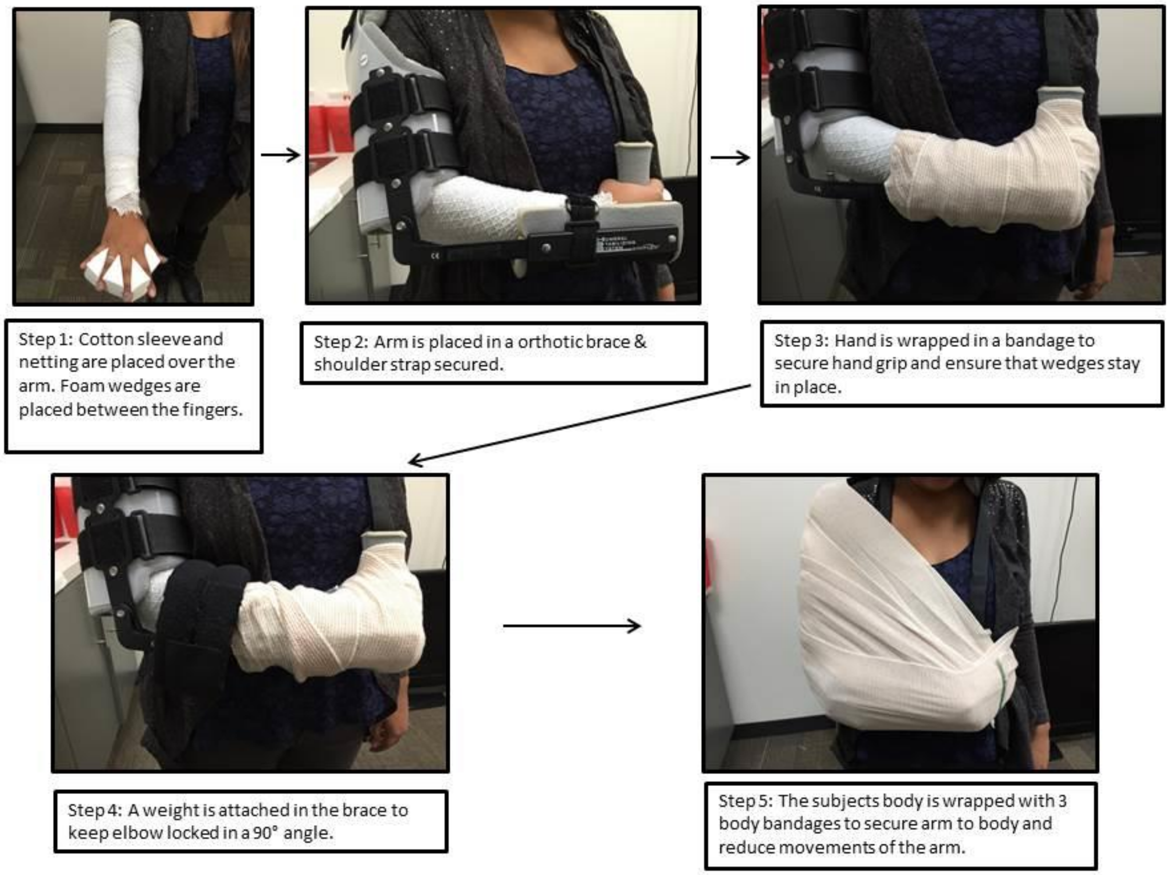
While seated with a response pad comfortably under their feet, participants performed a “pre” test, where they were presented first with a circle (4-6 s), then a fixation cross which alerted participants that the trial was about to start (500 ms), followed by the instructor-tool image (3 s). Prior to the experiment, the participant was told the following: “The images on the screen will show you any of the tools you have just trained with, being used by either a left or right hand instructor, and can be shown either in an egocentric (as if you yourself are using the tool) or allocentric (as if you were watching me use the tool) perspective. On the image there will be a red arrow located on the wrist of the actor. Based on the direction of the arrow, you will need to simulate in your mind which way the hand is rotating, and answer if the hand is driving the screw into the board, or is it pulling the screw out of the board.” If they thought the actor was inserting the screw into the board, they were instructed to indicate by pushing the left button with their left toe on the response pad. If they thought the actor was extracting the screw, they were instructed to indicate by pushing the right button with their right toe on the response pad. Based on the stimuli presented, this afforded an equal number of responses with the left and right hands without bias to the response hand matching the stimulus hand (i.e., a correct response would equally occur for the same number of left or right hand image actions). The participant was instructed to answer as quickly and accurately as possible from the onset of the image. If the participant did not respond before the 3s time period, a fixation cross appeared and no response was counted. There were 12 different image types. Each type was displayed twice in each of the two blocks that lasted approximately 12 minutes each. All images were presented in a pseudorandom order and correctness and latency of responses were recorded.

Immobilization

An orthosis was used to immobilize the right arm. The arm was fixed in a position that prevented flexion and extension of the wrist and elbow. Foam pads were placed between the fingers in order to minimize tactile stimulation. In order to immobilize the participants’ dominant arm (Figure 7.1), first, a cotton sleeve and netting was placed over the arm followed by inserting foam wedges in between the fingers (Step 1). Next, the dominant (right) arm was placed in an orthotic brace that secures the arm in an “L” shape positioned in front of the body, a shoulder strap was secured around the opposite (left) shoulder and a plastic circular tube was placed in the middle of the participants' hand in order to lock out movement of the wrist (Step 2). An elastic bandage was wrapped around the participants' hand to secure the foam wedges and formation of the hand around the tube (Step 3). Next a weight was attached to the front of the brace, near the elbow, in order to keep the elbow at a 90 degree angle (Step 4). Lastly two elastic bandages were wrapped all the way around the participant securing the arm close to their body and to further reduce movement of the arm (Step 5). After the participant had been immobilized, they were instructed to go about their daily activities. However, they were told to avoid all strenuous activity, water and not to move their dominant arm at all. When they returned to the lab after 8 hours, they were again set up with the EEG cap and performed a "post" action understanding task using the same images as used in the pre-test.

Analysis

Behavioral responses were recorded over two blocks of trials. All responses were recorded with Stim2 version 4.0 (Neuroscan 2003, El Paso, TX). Data sets were imported into Excel spreadsheets and organized by type into blocks. For each block, the response and latency average were calculated for each participant and every image type excluding any trials that the participant missed. Overall, there was no difference in missed trials for any image type (*p*= .387). All block averages were compiled into a grand average for each image type. Averages were then entered into IBM SPSS Statistics 19. A 2-way multivariate ANOVA (MANOVA) was computed with factors perspective



Step 1: Cotton sleeve and netting are placed over the arm. Foam wedges are placed between the fingers.

Step 2: Arm is placed in a orthotic brace & shoulder strap secured.

Step 3: Hand is wrapped in a bandage to secure hand grip and ensure that wedges stay in place.

Step 4: A weight is attached in the brace to keep elbow locked in a 90° angle.

Step 5: The subjects body is wrapped with 3 body bandages to secure arm to body and reduce movements of the arm.

Figure 7.1: Procedural steps to immobilize the dominant arm.

(egocentric and allocentric) x hand of actor (left and right hand). Where appropriate, t-tests were used to identify interaction effects between the different image types. For t-tests, significance was assessed at $p<.05$ with Bonferroni correction for all comparisons.

Using a customized Neuroscan script, neural data were epoched, baseline corrected to the first 500 ms (-1000 to -500 ms), band pass filtered from 8-10 Hz, and a linear detrend was applied. The data were then sorted into the 4 conditions and a customized MATLAB (Mathworks, MA) script was used to compute the imaginary coherence for each image type. Mu band (8-10 Hz) was chosen for this study based on the findings in chapter 4. Coherence is a measure of the linear dependency of two signals at a specific frequency. Imaginary coherence is a reflection of true brain interaction and is sensitive to synchronization of two processes that are phase lagged to each other in a specific frequency (Nolte et al 2004). The temporal window of coherence analysis of interest was based on the detailed theoretical methodology in previous work (Wheaton et al., 2008). This work focused on the time of ~400 ms (280-526 ms, centered at 408 ms), based on prior studies showing that neural responses related to comprehension of skilled action occur within the first 400 ms of the image presentation (Mizelle & Wheaton, 2010). Additional time windows between 400ms until behavioral response were analyzed for the immobilization condition to assess any additional effects immobilization may have on neural response. Further, prior studies have suggested that the mu band is related to action encoding properties that we are seeking to evaluate (Pfurtscheller & Neuper, 1997; Pineda, 2005). More specifically, the mu band has been shown to reflect changes in power over the sensorimotor cortex during action observation (Cochin et al., 1998; Pineda, 2005).

The parietal-premotor network is the focus of the chapter, primarily because of the work by Goldman-Rekic (1989) that showed distinct connectivity between the parietal-premotor areas by injecting a radio tracer dye into areas of the posterior parietal cortex of a Rhesus monkey. This study clearly depicts the left and right parietal and premotor areas are anatomically connected, however there are no direct connections to the motor cortex (Cavada & Goldman-Rakic, 1989). Therefore, this chapter will focus on the electrodes that are analogous to the same neural regions in humans. Based previous work (Cusack et al., 2012b; Wheaton et al., 2005), the electrodes used were as follows: left parietal, TCP1, P5, P3, P1, P3P; right parietal, TCP2, P2, P4, P6, P4P; left premotor, C1A, C3A, C5A, F1, F3; and right premotor, C6A, C4A, C2A, F4, F2. For all possible channel pairs, coherence was calculated within the mu band (8-10 Hz) using a Hanning window filter and non-overlapping 256 ms time windows across the time interval of the entire epoch based on previously published methodology (Wheaton et al., 2005) relative to a 512 ms baseline before the onset of the warning cue. This results in an electrode array, where coherence from any single channel was calculated with respect to all other channels. Imaginary coherence was calculated for all subjects and averaged to assess lateralization of parietofrontal coherence in the left and right hemisphere.

To counter intersubject variance, subject data for all possible channel combinations was resampled 500 times according to the bootstrap procedure (Mizelle & Wheaton, 2010a; Natraj et al., 2013). This was applied to each condition and for each hemisphere. To assess the dynamics of the parietal-premotor network and the possible effects of immobilization, percent change from baseline was calculated for all time windows between image onset to average behavioral response time. The threshold for statistical significance was held at $P<.005$ for all ANOVAS.

Results

Behavioral

Latency

For latency of response time, there was a main effect of perspective ($F(1, 24)= 58.35$, $p<.05$). When participants look at egocentric images, they respond statistically significantly faster compared to allocentric images (Figure 7.2 a). There was additionally a main effect of time (*F*(1, 24)= 31.43, *p*<.05) where the participants responded statistically significantly faster post immobilization.

Accuracy

Accuracy (percent correct) was also evaluated for each image type. There was a statistically significant main effect in percent correct due to perspective (*F*(1,24)=15.9, *p*<.05), with participants responding more accurately overall to egocentric versus allocentric images (Figure 7.2 B).

Cortico-cortical Coherence in Regions of Interest

Before Immobilization

Before immobilization, there were statistically significant differences in imaginary coherence between the left and right hemisphere parietal-premotor areas. When subjects viewed a right hand in an egocentric perspective, there was a greater percent increase in imaginary coherence from baseline in the contralateral left hemisphere compared to the right hemisphere. When they viewed a left hand in an egocentric perspective, there was a greater percent increase in imaginary coherence from baseline in the right hemisphere. For both left and right hands in an allocentric perspective, a greater percent increase in imaginary coherence was found corresponding to the hemisphere that followed a mirror matched limb strategy. Figure 7.3, before immobilization of the dominant arm (blue), shows the percent change in imaginary coherence from baseline in the parietal-premotor region of interest. (A) is representative of the parietal-premotor connections in the left

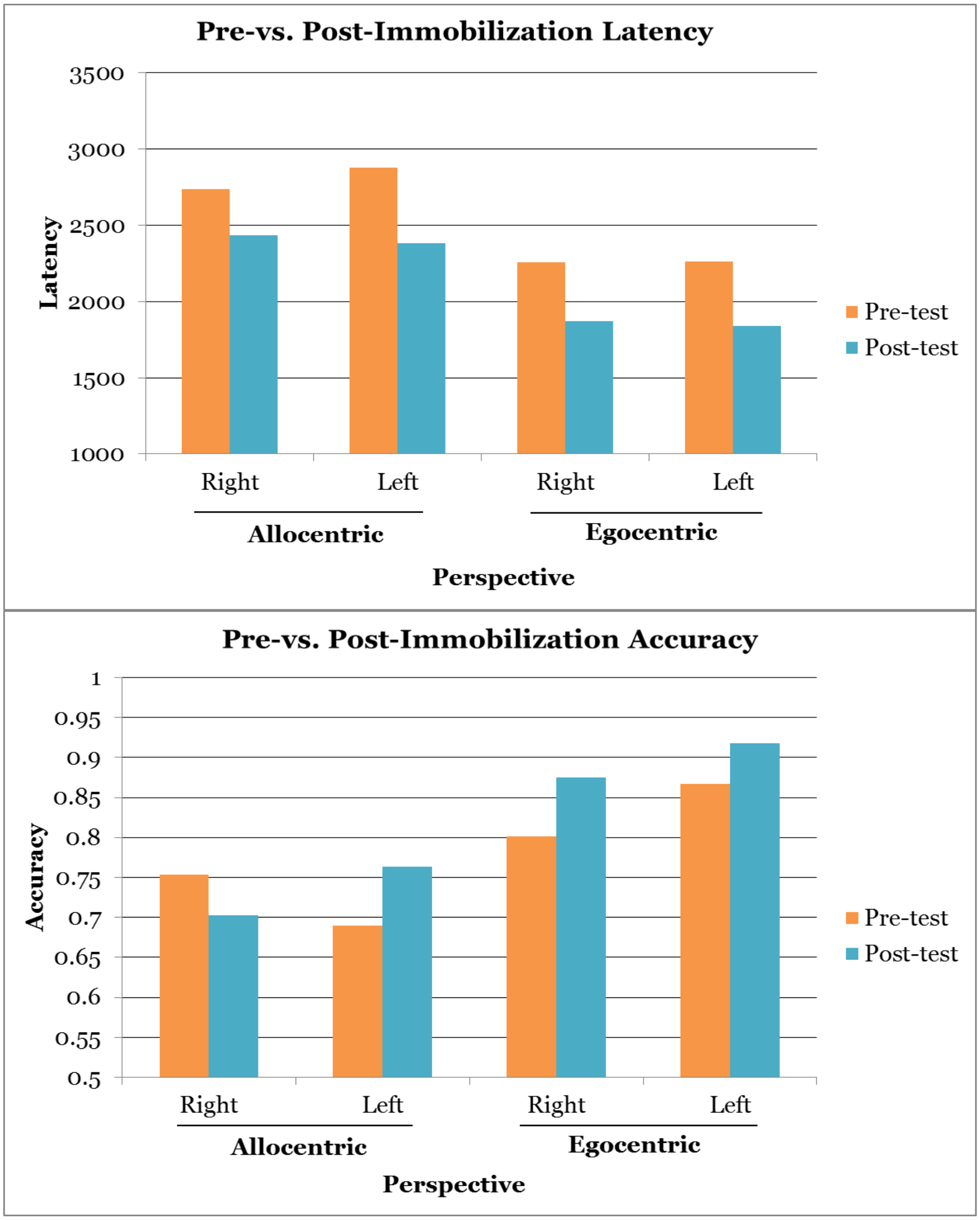


Figure 7.2: Bar graphs show average latencies (a) and accuracy (b) pre- and post-immobilization, with egocentric images having faster latencies and highest accuracies compared to allocentric images. Results shown are statistically significant ($p<0.05$).

hemisphere, and (B) shows the connections in the right hemisphere. The largest percent increase in imaginary coherence would suggest that, dependent on the hand seen, the contralateral hemisphere drives the motor simulation.

After Immobilization

After eight hours of immobilization, percent change in imaginary coherence from baseline was assessed at the same time window (408 ms) as before immobilization. In the left hemisphere for all conditions (Figure 7.3 A), there was a decrease in imaginary coherence from baseline. Contrastingly, there is a corresponding increase in imaginary coherence for every condition in the right hemisphere (Figure 7.3 B). However, the increase that was observed was smaller in magnitude than the percentage increase observed in the before immobilization condition and did not differ statistically significantly from baseline.

To establish if there were any additional differences in imaginary coherence between the hemispheres, percent change from baseline was calculated at each time interval from onset of image to average behavioral response for the condition. At a later time window (920 ms), peak change in imaginary coherence to the left and right hemisphere was observed. In Figure 7.3 B, for all conditions after the immobilization period (red), there was an increase in imaginary coherence from baseline to the right hemisphere. Contrastingly, in the left hemisphere (Figure 7.3A), all conditions showed a decrease in imaginary coherence from baseline.

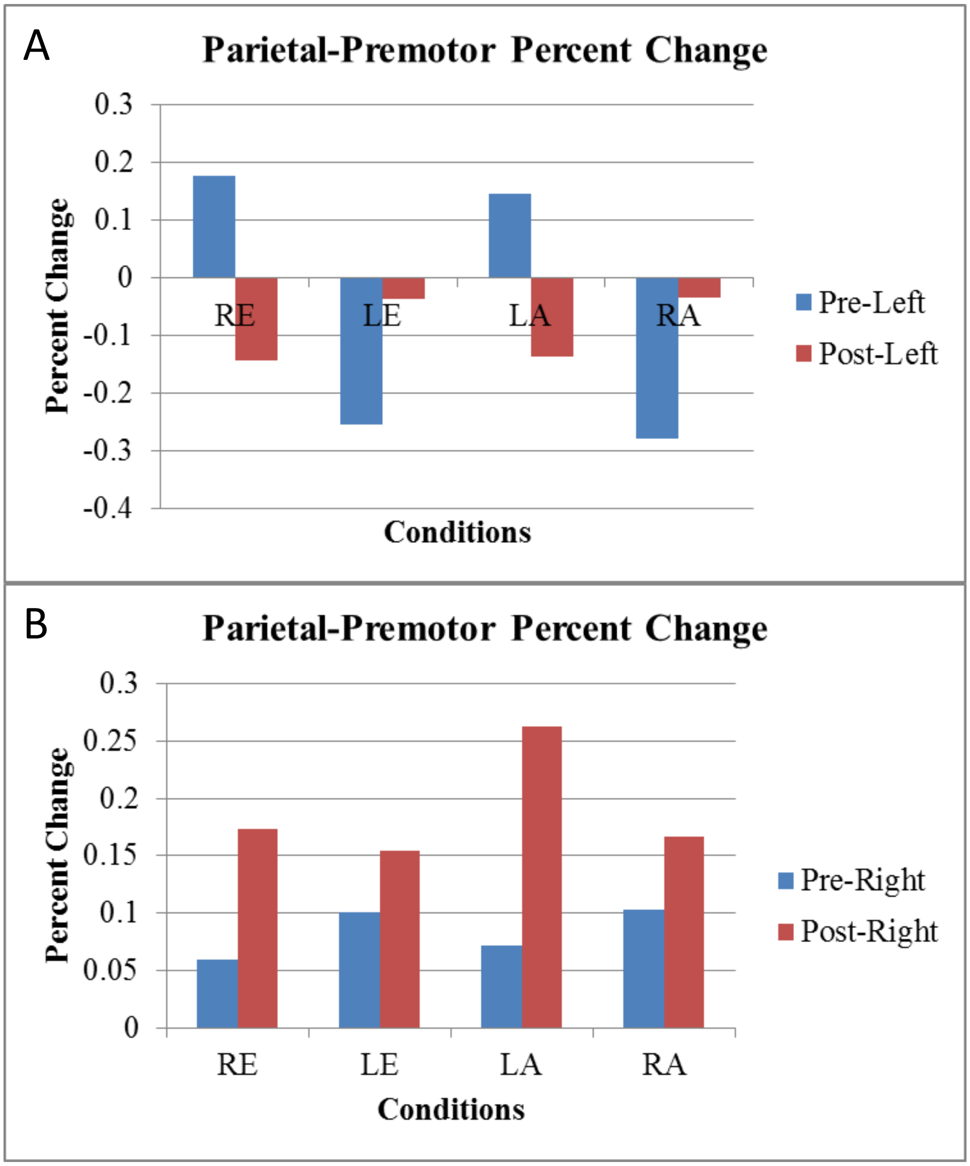


Figure 7.3: Illustrates the percent change in imaginary coherence in parietal-premotor neural networks in the left hemisphere (A) and in the right hemisphere (B). Before immobilization (blue) and after 8 hours of immobilization (red) are shown in both graphs for all four conditions. Condition abbreviations are as follows: RE= right hand egocentric, LE= left hand egocentric, LA= left hand allocentric, and RA= right hand allocentric.

Discussion

This study illustrates the importance of sensory feedback on action observation networks. The simple addition of an orthotic for a short period of time can alter our neural networks, potentially making it more difficult for those with upper limb function loss to regain full function of their limb. This chapter showed there is a functional coupling of brain areas (specifically in the AO network) that are utilized to understand action. Before immobilization, we observed an increase in imaginary coherence in the parietal-premotor network specifically in the hemisphere that corresponded to which limb the subject was mapping to observed action, which also is identical to the results seen in Chapter 5. After limb immobilization, the networks are used in action observation under normal conditions no longer are dependent on which limb the subject mapped to. This could be due to the subject’s inability to map action to their right limb due to reduced sensory feedback and in turn the action observation network relies more heavily on the non-dominant motor hemisphere.

While the behavioral effects observed were not adverse to the immobilization, they did not get significantly more accurate from pre- to post-immobilization. This could be because of a learning effect from repeated exposure to the stimuli in the protocol. Future studies should take this in account and allow for a diverse set of stimuli that can probe behavioral effects more effectively. It is still possible that the lack of sensorimotor information can cause the action observation network to become less efficient or adapt another strategy to complete the action prediction task (Wilson et al., 2004).

Studies have suggested a dual pathway internal model for action understanding: the forward model and an inverse model (Kilner, 2011; Shippers & Keysers, 2010). As mentioned above, the inverse model follows a backward pathway by focusing on the action outcome and calculating the needed motor command. It includes what the sensory consequences could be dependent on the most likely executed action. In order for an accurate prediction of the action goal, predicted sensory information is compared to actual sensory information from the observer (Kilner, 2011). Forward and inverse models complement each other during action observation and have been proposed to transform observed action into simulating the action internally to predict the outcome (Wolpert et al, 2003). In a study done by Moisello et al. (2008), immobilization was shown to affect behavioral coordination of the upper limbs which suggest both feedforward and feedback mechanisms are affected (Moisello et al., 2008). When sensory information is impaired, the backward model can no longer use actual sensory information from the user. Because the arm is restrained, the reduction of sensory information from the orthotic could decrease the ability for the subject to mentally simulate the action.

These findings have important clinical implications because limb immobilization is used as a rehabilitation protocol in some cases to address upper limb functional loss. For example, in constraint-induced therapy, the unaffected arm is immobilized and training with the affected arm is utilized for recovery after a stroke (Reiss, Wolf, Hammel, McLeod, & Williams, 2012). Leipert et al. (1998) suggests that this type of therapy causes an increase in the motor map to the affected muscle and a decrease of the motor map to the immobilized limb. This current chapter suggests that immobilization does indeed cause cortical depression, however it additionally has an effect on the ipsilateral hemisphere. This suggests that immobilization has a global effect, even after a short period of time, on elements of the Action Observation Network, which is essential in rehabilitation of daily activities. These results highlight that more research needs to be conducted on the effects of limb immobilization on patients.

Conclusion

Altogether, this chapter shows that short-term limb immobilization causes cortical effects in healthy participants. More specifically, short-term upper limb immobilization caused a change in the neural networks to the contralateral hemisphere of the immobilized arm, and a corresponding shift in reliance to the ipsilateral hemisphere. In conclusion, even brief periods of sensorimotor deprivation can cause deficits in sensorimotor representations and could ultimately lead to a decrease in motor performance.

CHAPTER 8

CONCLUSIONS AND FUTURE WORK

Integration of Dissertation Findings

Investigating the neurophysiology behind our action encoding system offers a way of probing the underlying mechanisms regarding how we understand seen action. Being able to understand seen action is important for the ability to understanding the intent of others. The ability to mentally simulate action (motor simulation) is a strong proposal for how we interpret others' actions with implications for motor rehabilitation. Motor simulation is the capability to observe an action in another individual and re-enact that same action through mental rehearsal. The process of how we generate accurate motor simulations is proposed to be reliant on the context of the movement and sensory feedback from the limb.

The purpose of this dissertation was to expand basic neuroscience of the underlying neurophysiology for the motor simulation theory of how we interpret action. The action encoding mechanisms in the human motor system that were described in previous chapters suggest that the current rehabilitation process for action observation therapies may need to incorporate and utilize perspective and handedness variables in order to improve current protocols. Without acknowledging these variables, reactivating neural networks during rehabilitation after a stroke or amputation can be more difficult or counterproductive.

The goal of this dissertation was to understand the underlying neurophysiology of the motor simulation process during action encoding and create a neural-motor model for how actions are encoded. Generally, we hypothesized different strategies of action simulation between right and left-handed individuals. More specifically, we hypothesized that right-handed individuals would rely on their motor dominant left hemisphere for action encoding and motor simulation, while left-handed individuals will have a symmetrical pattern lateralized to their motor dominant right hemisphere.

In Chapter 4, results provided insight into how action-goals are encoded and interpreted by left and right-handed participants. Here, the encoding of action for different hands seen was not necessarily differentially encoded in left or right-handed participants in a way that would demonstrate behavioral differences. However, there was a benefit in the representation of actions encoded in the egocentric perspective for both participant groups. Additionally, left-handed participants who viewed allocentric action showed the pronounced deficit from other combinations of handedness and perspective. These results suggest observers may use different strategies to translate, or “map,” actions into their central sensorimotor representations in order to interpret action outcomes based on their handedness and perspective in which they see action.

Chapter 5 sought to provide insight into the neural mechanisms of motor simulations in right and left-handed participants. More specifically, this chapter explored if cortico-cortical network pattern existed and how it explains behavioral differences observed between right and left-handed individuals. The results showed differences in the hemispheric laterality of parietal-frontal network-based coherence patterns across participant groups. In the egocentric and allocentric perspective, right-handed participants map the action to the hand seen, but it was less clear with left-handed participants due to their bilateral projections.

In Chapter 6, cortico-muscular coherence was evaluated to determine if a neuromuscular strategy existed for motor simulations and action understanding. The purpose of this chapter was to further understand the physiology of motor simulation theory by determining whether there is a matching pattern of cortico-muscular coherence that corresponds with the laterality patterns observed when viewing action images. The main finding in this chapter was that right-handed subject's beta band cortico-muscular coherence decreased to the hand the participant was mapping the action to, respective of perspective and handedness of the actor. These results correspond with the cortico-cortical coherence pattern seen in right-handed subjects in Chapter 5. However, in left-handed subjects, results were not as clear. In conditions where they mapped actions onto their right hand, a decrease in cortico-muscular coherence was seen. Conversely, for conditions where observers mapped actions onto their dominant left hand, no statistically significant different was observed.

Lastly, in Chapter 7, cortico-cortical coherence patterns were once again explored in right-handed participants to observe how impoverished sensory feedback of the dominant limb impacts action interpretation strategies. Right-handed participants showed the same lateralization patterns as seen in the previous chapter before immobilization. However, after immobilization, a reduction in cortico-cortical coherence was seen to the dominant motor hemisphere (contralateral to the immobilized limb), and an increase in cortico-cortical coherence to the ipsilateral hemispheres. These results suggest that even brief periods of sensorimotor deprivation can cause alterations in sensorimotor representations and could ultimately lead to a decrease in motor performance.

In summary, these studies have shown behavioral and neural differences between right and left-handed subjects, thus suggesting that perspective and handedness are important factor in the process of understanding observed motor tasks. In all four studies, subjects judging the outcome of action images presented in the egocentric perspective were more accurate and responded more quickly when compared to action images presented in the allocentric perspective. This could be because the egocentric perspective facilitates easier action perception because it can be understood from an internal perspective within the subject.

As compared to right-handed participants, left-handed participants showed different, non-symmetrical, patterns of motor simulation and action encoding. This discovery alone suggests that the inclusion of left-handed participants should be included in neuroimaging studies. Being able to highlight the differences in the two populations will improve the understanding of lateralization patterns in the brain. This dissertation also presented a novel approach of how to observe perturbations in the cortico-muscular network. The use of a dual task allowed for changes in the cortico-muscular network to be observed and ultimately reflected the limb mapping strategy the subjects were using to understand action images. These findings suggest that those with different hand dominance could require different rehabilitation programs in order to most efficiently retrain the affected limb after upper limb functional loss.

Clinical Relevance

Coupling physical practice and the observation of everyday actions has been shown to be an effective rehabilitation strategy for those experiencing upper limb functional losses (Ertelt et al., 2007; Franceschini et al., 2010). Given that recent studies have reported positive action observation effects on the rehabilitation of motor deficits, this could be due to the ability to reactivate and strengthen combinations of motor areas and corticospinal pathways.

Current AON rehabilitation involves training the effected limb alongside of an occupational therapist (Lake, 1997). During a rehabilitation session, patients watch a video of their therapist perform an action related to daily living and then attempt to execute it in the same context. This series of studies suggest that the simplest perspective for action interpretation is in the egocentric perspective. In recent work, there is evidence that suggests amputees beginning to use a novel prosthetic device can benefit from action observation therapy that is performed with the matching limb of a prosthesis user (Cusack et al., 2012b). This dissertation, along with this study, suggest that during the beginning of action observation therapy for amputees, action observation should begin egocentrically. Further expansion of this suggested paradigm would be to include the allocentric perspective in action observation therapy as the patient progresses, as a second dimension of difficulty in order to mimic real world scenarios.

The results in this dissertation are not intended to substitute current rehabilitation processes, but rather combine these findings and incorporate them with current practices to improve rehabilitation progression. Future studies may possibly include implementing matched limb action observation therapy training sessions along with traditional protocols. This future work will expand the basic neuroscience of action simulation and allow us to create a model for understanding the neurophysiology of action encoding based on limb dominance and perception of limb observed.

Future Motor Control Studies

Handedness

This dissertation has mapped out the neurophysiological mechanisms during action understanding for right-handed people. For left-handed people it was shown that different cortico-cortical and cortico-muscular patterns are engaged, however, there is still more to explore with left-handed subjects. Future studies should consider being more restrictive on the handedness score. Including only subjects who would be considered ‘extreme’ on the Edinburgh handedness scale could be further explored to determine if there are any variations within subject populations. Due to left-handed participants often being forced to do tasks with their right hand, it could influence the way they perceive actions to be more like right-handed participants.

Including left-handed individuals in future neuroimaging and motor control studies should be considered as well, because as shown in previous chapters, their neural networks are not symmetrical to right-handed individuals. Including left-handed participants would provide additional and unique knowledge of neural networks that further explain how the brain works.

Due to the bilateral neural networks found in Chapter 5, future studies on the transferability of learning a task with the dominant vs. non dominant hands should be conducted with left-handed participants. Results could show that it would be easier for a left-handed person because they can make the switch between dominant and non-dominant hand more efficiently. Additionally, this dissertation focuses primarily on unimanual dynamic actions; however there are also other types of action that can be expanded on in future studies. One proposal is to determine if action encoding differs when seeing dynamic versus stabilizing tasks. For example, dynamic tasks typically are performed with a person’s dominant hand and the non-dominant hand performs stabilization for the task. How would the action encoding process be different if you observed bimanual action tasks or tasks that involved the reversal of hands performing dynamic-stabilizing tasks?

Expanding Population Groups

Children do not learn “left” and “right’ associations of the hand until 4 or 5 years of age. Including a younger population who has not learned this dissociation would be interesting to explore. Future work should investigate this population group using a similar dual bimanual motor task as was described in this dissertation. Testing children allows for the exploration of the validity in our proposed physiological model on children who are not consciously aware there is a distinct difference between the hands. According to the direct matching hypothesis, a person directly matching an observed action onto their body schema activates the same neural areas that store the motor representation as if they were performing the action themselves. If a subject is shown a motor act that they have never seen before, they do not have a stored motor representation (Pellicano, Thill, Ziemke, & Binkofski, 2011). Looking at novel motor acts, such as using tools, using children who do not yet understand intention would be an interesting way to longitudinally explore how we develop dissociations between the hands and ultimately understand the intentions of others.

In order to elaborate on clinical benefits, additional work including clinical populations, specifically expanding the work to include those who have upper limb functional loss, such as stroke and amputee populations must be done. Being able to test the methodology in a rehabilitation setting would enable the development of improved protocols and allow for behavioral testing to measure improvements.

Motor Simulations in Sports Rehabilitation

Motor simulation has recently grown popular in the area of sports medicine and sport psychology. Motor imagery has been shown to improve motor task performance and in the initial learning of new tasks (Feltz DL, 1983). While the application of motor simulations has been used in a variety of ways, effectiveness has not been closely studied until recently. Hall et al. (1990) did a large study in a variety of sports and asked athletes to report their use of motor imagery (Hall CR, 1990). They found that skill level was proportional to the amount of imagery they used daily. If these techniques are used to improve motor performance, if this effect generalizable to injured athletes who have suffered an injury and need to be immobilized? If immobilization indices changes in cortical representations, perhaps motor simulation rehabilitation can be used on this population to reduce the effects of being immobilized for a prolong period of time.

Future Clinical Applications

The results in this dissertation could be incorporated with current practices to improve rehabilitation progression in the upper limbs. Future studies may possibly include implementing matched limb action observation therapy training sessions along with traditional protocols. Coupling physical practice and the observation of everyday actions has been shown to be an effective rehabilitation strategy for those experiencing upper limb functional loss (Ertelt et al., 2007; Franceschini et al., 2010). Recent studies have reported positive action observation effects on the rehabilitation of motor deficits, which could be due to the ability to reactivate and strengthen combinations of motor areas and corticospinal pathways.

Current rehabilitation for stroke survivors involves training the effected limb alongside of an occupational therapist. During a rehabilitation session, patients watch their therapist or a video of their therapist perform an action related to daily living and then attempt to execute it in the same context. A study by Ertelt et al. (2007) described the benefit of AO on motor rehabilitation for stroke survivors (Ertelt et al., 2007). In this study, one group of subjects participated in AO therapy where they watched videos of actions being performed and were then asked to physically practice the action themselves. The second group was a control group who watched vides that contained abstract shapes performing the same actions. While both groups improved compared to their baseline, those who were in the AO therapy group showed a greater improvement in motor function. This literature complements Cusack et al. (2011) work that showed matching limb observation plays an important role during the planning of motor tasks. They showed that subjects that were trained with a matching limb, compared to a mismatched limb showed reduced movement variability after learning task and behavioral and neural advantages. Taken together, these studies suggest that in AO therapy, the most beneficial protocol would be to make the videos match the patients affected limb to see the greatest results. Based on results from this dissertation, AO therapy should also take into account the perspective in which the videos are being shown. An egocentric perspective would model closely what the participant observes as they perform the task themselves. Creating a match between the AO therapy video and the participant could show greater improvements, while allocentric perspectives can be utilized later to add a level of complexity to challenge the participant.

This dissertation suggests that the simplest perspective for action interpretation is in the egocentric perspective and it is important to take into account the handedness of the patient. This would suggest that during the beginning of rehabilitation, action observation should always begin egocentrically and the therapist should always match the affected hand, and as the patient progresses, possibly incorporating allocentric perspectives secondary in order to mimic real world scenarios.

APPENDIX A

Edinburgh Handedness Inventory[1]

Your Initials:_____________
Please indicate with a check (✓) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✓✓).

If you are indifferent, put one check in each column (✓ | ✓).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

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[1] Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsycholo lgia*, *9*, 97-113.

APPENDIX B

Tool Familiarity Questionnaire

Please rate how familiar the following tools are based on the chart provided, as well as answer any additional questions found below.

Response	Familiarity
1	*Unfamiliar*
2	*Somewhat Unfamiliar*
3	*Somewhat Familiar*
4	*Familiar*
5	*Very Familiar*

Traditional Screwdriver

How familiar are you with the following tool? __________

Have you ever used this tool before? _________

Rotational Screwdriver

How familiar are you with the following tool? __________

Have you ever used this tool before? _________

Ratchet

How familiar are you with the following tool? __________

Have you ever used this tool before? _________

Wrench

How familiar are you with the following tool? _________

Have you ever used this tool before? ________

Push Screwdriver

How familiar are you with the following tool? _________

Have you ever used this tool before? ________

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VITA

RACHEL LOUISE KELLY

Ms. Kelly was born in Huntingdon, England. She attended public school in Toccoa, Georgia, and received a B.S in Psychology from the Georgia Institute of Technology, Atlanta, Georgia in 2009. She was admitted to Georgia Institute of Technology to pursue a doctorate in Applied Physiology in 2010 where she worked in the Cognitive Motor Control Laboratory. When she is not working on her research, Ms. Kelly enjoys playing along the river with her dog Goldie, cooking, and kickboxing with her sister.