Emergence of cortical activity patterns as infants develop functional motor skills

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Kinesiology)
in the University of Michigan
2016

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Service to others is the rent you pay for your room here on earth.

~Muhammad Ali

Acknowledgements

I am privileged to have worked with the best and those who have truly pushed me to complete this dissertation and inspire me to move forward. I was able to complete this dissertation and earn my degree only with the support and guidance from a village of people. I would like to thank the Developmental Neuromotor Control lab, Cheryl Drenning, Do Kyeong Lee, Sandra Saavedra, and Jennifer Sansom, for all of your support and guidance.

Bev: Words are not enough to express my utmost appreciation for all that you have done for me. I am grateful for your tremendous guidance and mentorship. I owe all of my success from here on forward to you, and I hope to expand all that you have done for the field.

Sean: I sincerely appreciate your mentorship and taking me on as a student. Your input and support has influenced me and certainly improved my research and development as a scientist. Thank you for taking me under your wings and navigating through this program.

Ioulia: I cannot thank you enough for your patience and leadership as Director of the fNIRS lab. Your feedback on my work has shaped it to what it is today. Without your leadership of the lab, none of my success would have been possible.

John: I could not be more grateful for your contributions to my dissertation. From the early stages, your words, thoughts, and insights have all been stimulating and the fuel to push my projects. Thank you for your contributions and conversations.

Maria Mercedes Arredondo, you have been my rock through this journey. Your support has allowed me to be who I am, as a student, researcher, and person. Thank you thank you thank you with love. ~You are my sunshine, my only sunshine~ I love you so so much.

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Abstract

Despite the careful examination of the developmental changes in overt behavior and the underlying muscle activity and joint movement patterns, there is very little empirical evidence on how the brain and its link to behavior evolves during the first year of life. The dynamic systems approach and theory of neuronal group selection provides a framework that hypothesizes the development of the CNS early in life. However, the direct examination of the changes in brain activation that underlie the development of functional motor control in infants have yet to be determined or tested.

The goal of my dissertation was to use functional near-infrared spectroscopy (fNIRS) to document the changes in brain activation patterns as infants acquired functional motor skills. My studies show that fNIRS is a viable and useful tool to examine brain activity in the context of infant movements. My findings demonstrate that as the behavioral and motor outcomes improve, the underlying neural activation patterns emerge. When functional motor skills are unstable and not fully functional, larger areas of the broad brain regions are recruited. As the skills become more reliable and functional, the brain activation patterns become refined and show an increase in strength of activity.

The results from the studies in my dissertation take an important first step of describing the typical neural patterns that emerge with functional motor skills early in life.

This work will help future studies build the body of empirical evidence that will improve our knowledge regarding the developing link between brain development and behavior. Finally, these studies provide foundational knowledge to better understand the atypical development of the CNS in those with disabilities.

Chapter I: Introduction

1.1 Contemporary theories of Motor Development

During the first year of life, an infant acquires many motor skills such as reaching, grasping, crawling, scooting, sitting, and stepping. The emergence of these skills are some of the most dramatic and impressive changes observed during this period. However, despite advances in technology, scientists have yet to discern the neural activation patterns that underlie the emergence of such overt behaviors. Current neuroscience theories and empirical data demonstrate the bidirectional relationship between developmental changes in behavior with changes in brain activation patterns. Moreover, balancing behavioral evidence with direct neurological measures is critical to improve and develop new avenues to early intervention for those with developmental disabilities.

Refined measures of motor behavior afforded by advancements in motion tracking and electromyography enabled improved ways to test a series of overlapping theories that argue in favor of an experience dependent emergence of motor skills. The theories include dynamic systems theory (Thelen & Smith, 1994), developmental systems approach (Gottlieb, Wahlsten, & Lickliter, 1998; Spencer et al., 2009), and dynamic field theory (Wiebe, Morton, Buss, & Spencer, 2014). These theories all capture the same central tenet; new skills (patterns of behavior) emerge with experience as multiple subsystems engaged during performance (e.g. intrinsic and extrinsic dynamics, environment, and task) converge to achieve a goal. Support for these theories is derived from observations that actions are self-organized and softly assembled rather than hard-wired and predetermined (Thelen & Smith, 1994). Thelen and colleagues demonstrated the plasticity of infant stepping by showing the persistence of similar lower-limb kinematics in various postures, such as supine kicking and stepping while supported over a treadmill (Thelen & Ulrich, 1991; Thelen, 1985), even when stepping was supposed to be inhibited by the proposed maturation of the higher brain centers. Importantly, the emergence of stepping like reaching and all other functional skills has been attributed to converging improvements in multiple systems (e.g. muscle strength, neural transmission speed, and sensory development), exploration and goal-directed practice.

First successful reaches emerge around 4 months of age. In the months and weeks leading up to the emergence of this behavior, infants make repeated attempts of arm movements directed towards the object before them. This is known as prereaching and is characterized by increased co-activation of typical agonist/antagonist muscles, increased errors or less contact with the target object, and increased variability in the patterns of movement as they move their arms toward a toy. Over time, infants gain more experience and success in reaching, the muscle activation patterns is refined and the behavior becomes more reliable, accurate, and adaptive (Thelen et al., 1993; Thelen, Corbetta, & Spencer, 1996). Concurrently, the development of eye, hand, and head control contribute to the assembly of subsystems for reaching to emerge (Thelen et al., 1993). As voluntary and purposeful reaching becomes increasingly successful, this behavior enables infants to obtain and manipulate objects, and explore their immediate environment, thereby accessing new types of information, which has been shown to enhance cognitive development (Bourgeois, Khawar, Neal, & Lockman, 2005), perception and memory (Needham, Barrett, & Peterman, 2002; Needham, 2001)..

The same dynamic systems framework supports the emergent patterns of muscle activity as cruising and walking begin to emerge around 10 months. In a series of studies, Ulrich and colleagues (Chang, Kubo, & Ulrich, 2009; Teulier et al., 2009) showed that infants and toddlers with typical development produce many unstable combinations of muscle activation when stepping while supported over a treadmill across the first year of life and into the first few months of independent walking. More organized and efficient muscle activation patterns emerged which underlie the refinement in control and limbs reflected by improvement in kinematic behavior. Interestingly, stepping in this context up is not a behavior that they practice in their everyday activities. Thus, the researchers argue that each time infants were tested, they responded with context-specific exploratory behavior, which reflects a goal to overcome the instability of having their legs moved backward. After 6 months of independent walking experience, toddlers with typical development showed efficient synergies of muscle activation (Chang et al., 2009).

At the core of all the contemporary models of infant motor development discussed above is the concept of experience dependent neural plasticity. To date, the dynamic and complex development of the nervous system supporting the emergence of reaching and stepping has only been inferred on the basis of movement kinematics, kinetics and overt outcomes. Direct measures of the concurrent neural changes that change with the emergent behaviors do not exist. Moreover, the hypothesized bidirectional interaction of activity on brain organization and the brain’s changes affecting the behavior has been tested and hypothesized in adults, but yet to be empirically tested in infants. As a result, the hypothesized maps widely accepted in adults, may or may not exist for infants, but may emerge dynamically. Thus, the initial step must be to map the typical neural activation changes in the developing brain that emerge as infants develop functional motor skills Then, future work can test the dependency of the relationship between the CNS and the emergence of functional motor skills. For example, directly examining the neural contributions to the emergence and production of a functional motor skill in infants with typical development will provide a foundation to understanding how this differs from infants who exhibit significant motor delays and deficits. Furthermore, such findings will allow researchers and clinicians to understand how current interventions and therapies are changing the functional activation patterns of the CNS its relationship to the motor impairments. Much like how advances in motion capture and electromyography provided deeper insights and evidence for the contemporary theories of motor development, advances in neuroimaging have the potential to yield the critical empirical evidence that will shape future theories

1.2 Neuroimaging as a Tool to Study Development

Investigation of the neural basis for the emergence of new behaviors during infancy has been hampered by the significant constraints posed by traditional neuroimaging techniques. Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are commonly used for studying motor areas in adults but both techniques are extremely sensitive to movement related artifacts. Movement artifacts are minor inconveniences in adult studies, because participants are able to listen to follow instructions and perform tasks without moving their head and uninvolved limbs. In infants, extraneous movement is quite problematic given the large number of trials required to obtain a small number of usable data. The significant noise and narrow confines that exist in the fMRI environment are also prohibitive to functional studies of the infant brain because babies cannot tolerate them while awake. In addition, safety concerns related to the radio frequency gradients and acoustic noise of an fMRI scan have yet to be fully investigated in adults let alone the potentially more susceptible infant population. While the environmental and safety concerns are not as prevalent with EEG, the time required to prepare recording electrodes and the potential for irritating the scalp can cause infants to become fussy before data collection can be completed. Further, somatic sensations associated with electro-conducting gels can agitate infants making them less cooperative. However, most important with regard to the use of EEG is that the summation of neural activity from multiple generators in the brain at a single electrode makes it difficult to localize temporal changes to specific regions of the brain (Michel et al., 2004; Pascual-Marqui, 1999).

Functional near-infrared spectroscopy (fNIRS) has become an increasingly popular choice for a neuroimaging technique among developmental scientists. It has greater spatial resolution than EEG and higher temporal resolution than fMRI, thus, fNIRS enables researchers to address and identify regional specificity in the developing brain. fNIRS uses near-infrared light to measure changes in cerebral oxygenation. Additionally, the fNIRS technology utilizes near-infrared light between 690 and 830 nm wavelengths. In this range, light is minimally absorbed by water and is mostly absorbed by the chromophores, oxygenated and deoxygenated hemoglobin (HbO and HbR, respectively). Near-infrared light is delivered via fiber optic cables that terminate into customized headgear. With this snug headgear system, fNIRS is more resilient to movement-related artifact than fMRI and is not subject to the same rigid head stabilization and supine posture requirements. The increased flexibility of fNIRS allows participants to assume a naturalistic posture relevant to more functional tasks, while tolerating large(r) body movements. The use of light also provides a unique opportunity to probe the thinner and developing tissues of the infant head. This allows the measurement of the cerebral cortex and cerebellum, which are located at much shallower depths than adults. Moreover, fNIRS is silent, safe, and the environment can be altered to maintain ecological validity (Lloyd-Fox, Blasi, & Elwell, 2010).

For the reasons outlined above, fNIRS is an optimal neuroimaging technique for studying early brain development in infants as they acquire and perform motor milestones. This thesis sought to exploit the advantages that fNIRS affords to test the contemporary theories of motor development and enhance our understanding of neuromotor development during the first year of post-birth life.

1.3 Regions of Interest for Motor Development

Across my series of studies, I investigated three brain regions of interest that are associated with motor learning and development. All these areas have been heavily studied in healthy adults (Halsband & Lange, 2006), but minimally in infants (Bell & Fox, 1996; Corbetta, Friedman, & Bell, 2014).

The primary motor cortex (M1) provides the primary descending output to the motor neurons controlling voluntary limb movements (Halsband & Lange, 2006). Researchers using fMRI have found evidence for a hypothesized somatotopic map of well learned fine motor tasks, such as finger tapping (Indovina & Sanes, 2001), hand clenching (Ehrsson et al., 2000), wrist flexion (Hidler, Hodics, Xu, Dobkin, & Cohen, 2006), and pointing (Filimon, Nelson, Hagler, & Sereno, 2007), simple flexion and extension of the ankle (Dobkin, Firestine, West, Saremi, & Woods, 2004) and elevation of the foot at the ankle (Lotze et al., 2000). In addition to motor neuron activity, goal-directed actions require the planning and online control of limb movements. Thus, additional areas of the brain, such as the prefrontal cortex (pFC) and cerebellum (Crbl), contribute to the motor outcome.

The anterior area of the frontal lobe known as the pFC is widely known for its role in attention and short-term memory. When people learn new movements and skills, the pFC, specifically their dorsolateral pFC (DLPFC) shows increased activity, particularly during the early stages of motor learning when errors are abundant. Goal-directed actions involve cognitive processes such as attention and decision making, more so during the these early stages of motor learning As individuals repeat and learn the task, activity in the DLPFC diminishes (Halsband & Lange, 2006; Pochon et al., 2001). As the behavior unfolds, it requires the monitoring and online feedback to maintain precision of the movement.

The Crbl contributes to the adaptive control of movements and overall posture. The Crbl, like the DLPFC, also shows enhanced activation in the early stages of skill acquisition reflecting the early, increased dependence on feedback (Doyon et al., 2002). As errors are reduced, Crbl activity decreases because close monitoring of feedback becomes less important once skills are mastered (Halsband & Lange, 2006). Recently, substantive evidence has accumulated showing that the Crbl plays a role in cognitive processes, such as attention and decision-making. Much like the pFC, activity in the Crbl is much higher when skills are being learned compared to when the movement is “automatic” or well-learned (Koziol et al., 2014).

Although the roles and contributions of each region have been described consistently in adults for the production of simple and well-practiced goal-directed movements, these have not been established for infants, for whom the brain is not as well organized and skills are nascent and developing. As infants learn to reach, for example, they explore many ways to control their limbs and other body parts in order to obtain their goal, the desired toy. Their action contexts are much different those of adults and, in particular, from the contexts of adult motor learning studies. For adults, tested new “skills” are manipulations or deviations of already well-learned and significantly practiced movements (e.g. motor sequence learning and motor adaptation). Infants attempt to reach many times before and after initial success and they take many steps with and without support over the first year before the skill is stable. All of these actions comprise a continued cycle of trial and error and acting and perceiving. Through these cycles, the activation patterns and contributions from each of the brain regions should change as infants gain goal-directed and self-initiated experience and learn to control and adapt their movements.

1.4 Specific Aims and Hypotheses

To describe the developmental changes in neural activation patterns as infants acquire new functional motor skills, I devised three studies. I began by establishing, using fNIRS, reliable measures of the adult M1 for tasks I wished to explore in infants. I followed this by examining the developmental changes in M1 activity as infants developed functional motor skills. Last, I explored, in addition to the M1, the pFC and Crbl to describe the patterns of brain activity across three different regions.

Specific Aim 1 (Chapter 2/Study 1): Before examining brain activation patterns of infants, there was a critical first step to understand hemodynamic activity, using fNIRS, in adults who are skilled performers. Thus, the aim of this study was to describe robust measures of hemodynamic activity of the primary motor cortex using fNIRS, as healthy adults perform different functional motor skills.

Hypotheses: During unilateral tasks, adults will show significant increase in oxygenated hemoglobin in the contralateral motor cortex. During bilateral tasks, adults will show significant increase in oxygenated hemoglobin in the bilateral motor cortex. Finally, the location of the sum of the changes in oxygenation during reaching tasks will be represented at distinctly different positions on the motor cortex compared to the stepping task.

Specific Aim 2 (Chapter 3/Study 2): To describe developmental changes in hemodynamic activity of the primary motor cortex as infants with typical development perform functional motor skills.

Hypotheses: During reaching, younger infants (5 to 7 months) will show significant increase in oxygenated hemoglobin from a disperse area of the primary motor cortex compared to older infants (11 to 13 months old). During stepping, older infants will show significant increase in oxygenated hemoglobin from a disperse area of the primary motor cortex compared to younger infants.

Specific Aim 3 (Chapter 4/Study 3): To describe the hemodynamic activity of the prefrontal cortex, primary motor cortex, and cerebellum as infants with typical development perform functional motor skills.

Hypotheses: Reaching - Younger infants will show significant increases in oxygenated hemoglobin from more channels covering the prefrontal cortex compared to older infants. Similarly, in the primary motor cortex, younger infants will show increases in oxygenated hemoglobin from more channels covering the bilateral primary motor cortex compared to older infants. In the cerebellum, younger infants will show increases in oxygenated hemoglobin from more channels compared to older infants.

Stepping – Older infants will show increases in oxygenated hemoglobin from fewer channels covering the pFC and Crbl. In the M1, however, older infants will show increases in oxygenated hemoglobin from more channels across the bilateral motor cortex, compared to younger infants.

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Chapter II: Motor Cortex Activity During Functional Motor Skills: an fNIRS Study

(Nishiyori, R., Bisconti, S., & Ulrich, B.D. (2016). Brain Topography, 29(1), 42-55.)

Abstract

Assessments of brain activity during motor task performance have been limited to fine motor movements due to technological constraints presented by traditional neuroimaging techniques, such as functional magnetic resonance imaging. Functional near-infrared spectroscopy (fNIRS) offers a promising method by which to overcome these constraints and investigate motor performance of functional motor tasks. The current study used fNIRS to quantify hemodynamic responses within the primary motor cortex in twelve healthy adults as they performed unimanual right, unimanual left, and bimanual reaching, and stepping in place. Results revealed that during both unimanual reaching tasks, the contralateral hemisphere showed significant activation in channels located approximately 3 cm medial to the C3 (for right-hand reach) and C4 (for left-hand reach) landmarks. Bimanual reaching and stepping showed activation in similar channels, which were located bilaterally across the primary motor cortex. The medial channels, surrounding Cz, showed significantly higher activations during stepping when compared to bimanual reaching. Our results extend the viability of fNIRS to study motor function

and build a foundation for future investigation of motor development in infants during nascent functional behaviors and monitor how they may change with age or practice.

2.1 Introduction

An emerging area of interest for developmental scientists is the neural basis of motor performance and learning of emerging skills. Practical and technological constraints have limited the contribution from traditional neuro imaging techniques like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). As a result, the neural basis of performance and learning in infants and young children has been based upon inferences informed by behavioral and muscular measures. The emergence of functional near-infrared spectroscopy (fNIRS) offers greater flexibility in both the behaviors and the populations that can be studied. Researchers have just begun to utilize fNIRS in areas of studies that were not possible before. Similar to fMRI, fNIRS measures changes in cortical oxygenation that reflect neural activity (Chance et al., 1998; Villringer & Chance, 1997). However, instead of relying on the differential magnetic properties of oxygenated (HbO) and deoxygenated (HbR) hemoglobin to infer levels of oxygenation, fNIRS exploits the differences in absorption of near-infrared light (Villringer & Chance, 1997). The use of near-infrared light rather than strong magnetic fields means that fNIRS can be employed in less restricted and more naturalistic environments to assess functional brain activation during dynamic motor tasks. Recently, researchers using fNIRS have shown the changes in brain oxygenation when participants performed a discrete motor skill (Ikegami and Taga 2008), walked on a treadmill (Koenraadt et al., 2014; Kurz et al., 2012), and balanced on a tilt board (Ferrari et al., 2014). These studies have strongly demonstrated the flexibility and adaptability of fNIRS to quantify cortical activity during various movements not possible in other neuroimaging techniques. The primary motor cortex (M1) has been an eminent target for investigating neuromotor behavior. In adults, it is well known that the M1 drives voluntary movements. fMRI studies have shown the blood oxygen level dependent (BOLD) response during several motor tasks, primarily with distal joints (e.g. wrist, hand, or finger) to quantify a hypothesized somatotopic map and kinetic properties during simple well-learned motor tasks such as finger tapping (Indovina and Sanes, 2001), hand clenching (Ehrsson et al., 2014), wrist flexion (Hidler et al., 2006) and pointing (Filimon et al., 2007). The scanning environment, however, places a number of restrictions upon the motor behaviors that can be studied and how they can be performed, often limiting the ecological validity of the findings. The use of fNIRS continues to extend the boundaries of motor behavior research to examine cortical activity and allows researchers to determine spatial characteristics of activity during motor tasks. For example, Koenraadt et al. (2012) used fNIRS to identify differences in representations between hand and foot movements on the contralateral hemisphere of the M1. As hypothesized, hand representations were lateral to those of the foot. The tasks, however, were mixed-frequency tapping movements of the hand and foot. In addition, fNIRS measurements were only taken from the contralateral hemisphere of the M1, precluding findings about the ipsilateral cortex while performing the task or any potential bilateral activity associated with the unilateral tasks. Comparing hemispheric activity would elucidate the asymmetric cortical activity during unilateral tasks and bilateral cortical activity during bimanual tasks involving larger body segments and muscles. To identify the location of activation with multi-channel fNIRS data, the center of gravity (CoG) approach has become a useful tool (Koenraadt et al., 2012). The use of the CoG approach has been commonly used in transcranial magnetic stimulation (TMS) research to identify the CoG of the motor evoked potentials (Boroojerdi et al., 1999; Wassermann et al., 1992). For fNIRS data, the mean hemodynamic response values of all channels and the respective coordinates of the channels are considered to determine one location of activity (NIRS–CoG) for each task separately. The objective of the present study was to identify reliable measures of sensorimotor cortex activity as healthy adults reached for objects and stepped in place using fNIRS. Furthermore, because we measured cortical activity of the bilateral sensorimotor cortices, we aimed to identify ipsilateral activity and representations. We hypothesized that fNIRS data will reveal asymmetric activity in the sensorimotor cortex during unilateral tasks and symmetric activity during bilateral tasks. Moreover, we hypothesized that reaching tasks will show increased changes in cortical oxygenation in lateral areas compared to stepping in place, which is expected to show changes in the most medial areas.

2.2 Methods

2.2.1 Participants

The research protocol was approved by the Institutional Review Board at the University of Michigan Medical School (IRBMED). We acquired informed consent from 12 healthy right-handed adults (mean age = 23.41 ± 5.1 years, 8 females) who volunteered for our study.

2.2.2 Task

Participants performed unimanual (left and right) and bimanual reaching, and stepping in place during their onetime visit. For each type of reach and stepping, participants completed a minimum of ten trials, without any prior practice, that consisted of a task phase followed by a rest phase. All participants successfully completed all four tasks. For the reaching tasks, participants were seated and asked to assume the most comfortable posture with their feet touching the floor. The experimenter presented the objects within reach at midline and mid-chest level. We used small grip-sized objects (3 x 3 x 7 cm) for unimanual reaching and a large, but light object (61.5 x 0.6 x 31.5 cm) for the bimanual task (Figure 2.1). After participants grasped the object and brought it back to their laps, they were asked to release the object, which was followed by a 20-s rest interval. During the rest periods, participants remained quiet with their arms resting on their laps. The cycle was repeated for a total of ten trials. For the stepping task, participants stood upright and faced a monitor that displayed cues to step or to rest. Prior to the start of the stepping task, participants were instructed to mimic their natural walking style and to step at a comfortable pace (i.e. self-selected pace). Each stepping trial started with a 20 s rest, during which participants stood stationary with their arms at their side, followed by a 15 s stepping phase. The cycle was repeated for a total of ten trials. The participants did not know the duration of the task or rest phases to avoid any anticipatory movements.

2.2.3 Video Recording

To accurately identify the onset of a task, rest, and any undesired movements, we recorded the entire session using a digital video recorder (Canon, USA) sampling at 60 Hz. We used an audio signal to synchronize the video with the fNIRS data collection. This enabled us to map events onto the fNIRS data to accurately identify changes in hemodynamic responses related to the tasks.

2.2.4 fNIRS Data Acquisition

Hemodynamic responses during each task were recorded using a continuous wave 32-channel fNIRS system (CW6; TechEn Inc.) utilizing two different wavelengths (690 and 830 nm) sampling at 50 Hz. Near-infrared light was delivered via fiber optic cables that terminated in a customized plastic headgear. The headgear contained eight sources and 12 detectors approximately 3 cm apart, creating an 18-channel array. The headgear was positioned on the head following the 10–20 international system (Jasper, 1958) so that the center of the headgear was aligned with the vertex (Cz) and lateral channels covered the area around the C3 and C4 landmarks, which have been shown to detect activity that drives hand movement (Koenraadt et al., 2013). The medial channels surrounded the Cz landmark, which have been shown to detect leg activity (Koenraadt et al. 2014). Thus, in our configuration, the optodes were positioned over the sensorimotor cortex or Brodmann area (BA) 4 (Okamoto et al., 2004) to detect changes in both arm and leg activity as participants performed the respective tasks. Channels 1 through 9 were situated over the left, and channels 10 through 18 over the right hemisphere of the sensorimotor cortex (Figure 2.2).

2.2.5 fNIRS Data Processing

To convert the raw signal to optical density (absorption), we used the Homer2 data pre-processing software (Huppert et al. 2009). We employed a wavelet-based motion artifact removal algorithm to extract motion artifacts from the fNIRS signal (Molavi and Dumont, 2012). Changes in optical density were converted into changes in HbO and HbR using the Modified Beer–Lambert Law (Cope et al., 1988) with a partial pathlength factor (ppf) of 6.0. Next, we used a 0.02 Hz high-pass filter and a 0.8 Hz low-pass filter to remove any slowly drifting signal components.

2.2.6 Data Analyses

The heart rate was visually inspected on the raw data to ensure there were no differences between the rest and task phases. For each participant within each task, their ten trials were averaged to calculate the mean values for the rest and task period for each channel. To correct task data for baseline levels during the rest phases, we calculated the mean values during the respective rest phase and subtracted them from the mean values obtained during the task phase. Both the means for changes in HbO and HbR hemoglobin for the rest phase and that of the task phase from each channel were compared using the

Student's t test with the alpha level set at $p < 0.05$ to identify statistically significant changes related to the task. For each task, 18 t tests were performed; for this we employed a false discovery rate (FDR) to correct for multiple comparisons (Singh and Dan, 2006). The threshold for significance was set at $p < 0.05$ (FDR-corrected).

2.2.7 Laterality Index

To test for symmetry/asymmetry during tasks, we paired channels on opposite hemispheres, resulting in nine pairs, to calculate a laterality index (Solodkin et al., 2001; Tian et al., 2010) for HbO for each task by using Eq. (1).

$$L = \frac{oxy_l - oxy_r}{oxy_l + oxy_r} \quad (1)$$

In this equation, l represents the channel from the left hemisphere and r indicates the channel from the right hemisphere in the pair. The L value will reveal which channel between the pair showed a higher change during the task. Negative values indicate left-hemisphere dominant activations, while positive values indicate a right hemisphere dominant activation. Finally, to test for differences between channels that are activated in more than one task, we conducted a paired *t* test, with the alpha level set at $p < 0.05$.

2.2.8 NIRS-CoG

To identify one location of activity during a specific task, we used the NIRS–CoG approach. This approach was used in Koenraadt (2012), which discriminated the contralateral motor cortex activity of the hand and foot (Koenraadt et al., 2012). For our study, we calculated a NIRS–CoG for each task by using the mean responses from all 18 channels and the coordinates of the channels bilaterally. For both unimanual reaches and bimanual reaches, we calculated a NIRS–CoG for the contralateral and ipsilateral hemispheres. Moreover, for stepping, a single NIRS–CoG was identified. The NIRS–CoGs were calculated using Eq. (2).

$$X_{CoG} = \sum a_i X_i / \sum a_i \quad (2)$$

The ai represents either the HbO or HbR mean response amplitude at the corresponding coordinate, Xi. The Xi represents the x- or y- coordinate of the measurement point (the mid-point between the source and detector). For each subject, we averaged the X- and Y-CoG for HbO and HbR responses separately. The average X- and Y-CoG provided a single location of activity for each task. The x-axis represents the mediolateral direction, whereas the y-axis represents the anteroposterior direction. Moreover, the Cz location was set as the origin, the left hemisphere represented by negative values, and the right hemisphere represented by positive values. Positions anterior to Cz were represented by positive values, while posterior positions were represented by negative values. To test for differences in location across the NIRS–CoGs, we used a paired t test with an alpha level set at p\0.05. All statistical analyses were conducted using SPSS 21 (New York, USA).

2.3 Results

2.3.1 Changes in Oxygenation

First, we were able to detect task-related changes in oxygenation using fNIRS while adults performed functional motor skills. Moreover, no differences in heart rate were found between the rest and task phases. As shown in Figure 2.3, we identified task-related increases in HbO accompanied by slight decreases in HbR prior to processing our time series data. More importantly, prior to the start of the following trial, we observed decreases in HbO precluding any contamination of the activity by the previous trial. We found significant increases in HbO from select channels during the task-phase compared to the respective rest phase for each task (Figure 2.4), but did not find any significant differences in HbR (Figure 2.5). Overall, we found that during unimanual tasks, channels on the contralateral hemisphere showed significant activation. Moreover, during stepping and bimanual tasks, channels across both hemispheres showed significant activation.

Specifically, the channels located on the contralateral hemisphere showed significant increase during both right and left unimanual reaching. The t tests revealed that during unimanual reaching with the right hand, channels 5 ($p = 0.04$), 6 ($p = 0.02$), and 7 ($p = 0.04$), located on the left hemisphere, showed significant increase in HbO. These channels were approximately 3 cm medial to the C3 landmark. Similarly, during unimanual reaching with the left hand, channels 12 ($p = 0.04$), 13 ($p = 0.04$), and 14 ($p = 0.04$) showed significant increases in HbO. This set of channels was also located approximately 3 cm medial to the C4 landmark. During bimanual reaching, we detected significant activity in channels 5 through 14 (*p*s <0.05). This set of channels covered the bilateral sensorimotor cortices, while covering the most medial regions where significant activity was not detected during unimanual reaches. During stepping, we detected significant activity in channels 6 through 13 (*p*s <0.05). This set of channels was similar to those significant during bimanual reaches. A summary of the t statistics from the analyses can be found in Table 2.1 (HbO) and Table 2.2 (HbR). Finally, in Table 2.3, we show average traces of the hemodynamic response function (HRF) from each channel across all tasks. Here, we verify a robust increase in HbO accompanied by a slight decrease in HbR during the task phase followed by a decrease in HbO during the rest phase. Paired t tests of HbO in channels 8 through 11, which were activated during bimanual reaching and stepping, showed that these channels were significantly different $t(11) = 2.38$, $p = 0.04$; $t(11) = 2.42$, $p = 0.03$; $t(11) = 3.02$, $p = 0.02$; $t(11) = 2.62$, $p = 0.03$. That is, the most medial four channels (e.g. 8 through 11) were significantly higher during stepping compared to bimanual reaching.

2.3.2 Laterality Index

The laterality index values followed in line with our hypotheses regarding asymmetric and symmetric activity during unilateral and bilateral tasks, respectively. The index revealed that during unimanual tasks, the channels on the contralateral hemisphere showed dominant activation. During both bimanual reaching and stepping, the laterality index did not reveal any hemispheric dominance, thus showing bilateral activation (Figure 2.6).

2.3.3 NIRS-CoG

The NIRS–CoG for each task was identified on each hemisphere for both HbO (Figure 2.7) and HbR (Figure 2.8). For unimanual and bimanual reaches, the contralateral and ipsilateral NIRS-CoGs were identified on their respective hemispheres. We calculated one NIRS–CoG for stepping. We compared the NIRS-CoGs on the same hemisphere to identify any differences in representations in either mediolateral or anteroposterior directions.

The NIRS–CoGs for HbO of the left hemisphere showed that the bimanual representation was more medial and posterior than the ipsilateral activity during left hand reaches ($p = 0.01$ and $p = 0.01$, respectively) and the contralateral activity during right hand reaches (ps < 0.01). The stepping representation was significantly more medial than all three representations in this hemisphere (ps < 0.01). In the right hemisphere for HbO, the bimanual representation was more medial and posterior to the contralateral activity during left hand reaches ($p = 0.03$ and $p = 0.02$, respectively). The stepping location was more medial than all three representations in the right hemisphere as well (ps < 0.01). We found the contralateral activity during left hand reaches to be more anterior to that of stepping ($p < 0.01$). A summary of the pairwise comparisons is shown in Table 2.4.

We were unable to detect any significant differences among the locations of the representations based on the HbR data for NIRS–CoG (Table 2.5). As seen in Figure 2.8, the left hemisphere showed similar locations of representations as shown in Figure 2.7, with the HbO data. In the right hemisphere, however, we found the bimanual representation to be most lateral and the contralateral activity during left hand reaches to be more medial than the other manual tasks.

2.4 Discussion

We were able to determine the symmetric and asymmetric activity of the bilateral sensorimotor cortices using fNIRS during functional and dynamic motor tasks. It is well known that the neurons in the contralateral M1 drive isolated voluntary movements, much of which has been well studied in MRI studies with distal joint movements (Alkadhi et al. 2002; Lotze et al. 2000). Moreover, neuroscientists and clinicians continue to extend the boundaries of neuroimaging research to enable future investigation in clinical and pediatric populations and in behaviors difficult to measure using traditional techniques. More recently, researchers have used fNIRS as an effective tool to address the neural basis for motor behaviors that are extremely challenging to conduct in the MRI scanner. Unlike previous studies, our study measured the bilateral sensorimotor cortices, which enabled us to examine ipsilateral cortex activity.

The significant activity of HbO in our data supports the current understanding of motor control and extends our knowledge of cortical representations during dynamic and functional motor tasks. Our HbR results did not reveal any significant differences during the task phase. As observed in our mean responses (Figure 2.5), we generally see a decrease in HbR or below-zero mean, which follows the canonical HRF model. This pattern, however, was relatively inconsistent compared to the robust increases seen in our HbO data. Previous research has shown that a marked increase in HbO after stimulus onset is associated with an increase in blood flow accompanying increased neural activity, or otherwise known as the BOLD response (Huppert et al. 2013; Steinbrink et al. 2006). Although the smaller decrease in HbR accompanies the increase in HbO in these canonical models, the reports of HbR from various studies remain inconsistent and analyses have focused primarily on HbO data (Cao et al. 2015; Karim et al. 2013; Karim et al. 2012).

In addition, we were able to demonstrate and verify the canonical hemispheric dominance during unimanual reaching, revealed by the laterality index. A specific set of channels located just medial to C3 and C4 showed a marked increase in activity, while medial channels closer to Cz did not show significant activation. Our results showed that slightly more medial channels than those identified in Koenraadt et al. (2013), were activated during reaching, which involves proximal joints in combination with more muscles than wrist flexion or finger tapping. The selective activation of the channels only surrounding the arm representations demonstrates the location of regions responsible for reaching. Interestingly, however, we detected significant activity in the medial channels during bimanual reaching. In between cortical regions attributed to arm and leg regions controlling the motor neurons, lies the area responsible for the trunk muscles (Murayama et al. 2001). Furthermore, the same region of channels also showed significant activation during stepping, suggesting that these channels also covered the leg regions of the motor homunculus.

It has been suggested that the principal activity detected from the dynamic movement inherent to gait originates from trunk, arm, and upper leg movements (Koenraadt et al. 2012). Stepping in place requires the alternation of steps while maintaining balance. The offset of balance when one foot is in contact with the ground, while the other is off, is counterbalanced by the swinging arm(s). Furthermore, the legs must bear the body weight while counteracting against gravity requiring more effort from the legs than the arms. Such increased effort is reflected in our data, in which we observed the highest activity in the central channels surrounding Cz, and lower but significant activity in the lateral channels that were active during the reaching tasks.

During early development of motor control and recovery of motor function, the cortical contributions during a functional motor task are likely to come from different areas than those identified in healthy adults, where the skills performed are well learned. Thus, the contributions of both hemispheres of the sensorimotor cortices during functional motor tasks need to be established. Although the greatest change in cortical oxygenation was seen in the contralateral hemisphere, we separately calculated the ipsilateral NIRS–CoG to determine the location of the activity in the supporting hemisphere. In the present study, the representations of the arm, regardless of when the hemisphere is contralateral or ipsilateral to the reaching hand, were in similar locations, thus suggesting that during a right-handed reach, the NIRS–CoG in the right hemisphere is in the same location during left-handed reach. Previous research has shown that the cortical representations of ipsilateral hand movements are similar in location to that of the contralateral hand movements in the motor cortex (Ziemann et al. 1999). This suggests that a similar area is activated but perhaps inhibited by the corpus callosum, which has been identified to play an inhibiting role between the two hemispheres (Murase et al. 2004). During a unilateral movement, the ipsilateral hemisphere is inhibited which can be explained by hemispheric dominance (Vidal et al. 2014). In line with previous findings our results show that the ipsilateral activity, although small and inhibited, seems to gravitate towards the arm region.

The cortical data in the present study reflect established motor control, as the tasks in the present study were welllearned basic motor skills that healthy adults can perform without fail. The pediatric population may show more varied cortical activity, as the motor control is improving and developing over time. Furthermore, studies can now focus on more dynamic and functional motor tasks as a paradigm to investigate the cortical organization during development instead of simple movements that are infrequently used in everyday activities. Our findings identified inhibited cortical activity, as a result of established motor control, but open the door to questions regarding how and when this inhibition comes on-line. Furthermore, the successful discrimination between the representations provides a foundation for future research investigating the neural basis for the emergence and development of functional motor control.

Although we were able to provide reliable measures, our current study had limitations. First, we did not use structural MR images from the participants or an average template to localize our headgear. Although this opens the concern regarding the precision of our channel locations, our approach was to rely solely on fNIRS technology and the international 10–20 measurements. We, like many previous studies that did not use other means to localize channel positions, took careful head measurements to accurately locate the international 10–20 landmarks for each participant. For these reasons, we moved forward by using methods suggested by previous research who have established the reliability of the head measurements and landmarks as references for the position of our headgear (Okamoto et al. 2004; Tsuzuki et al. 2007). Second, we did not utilize any electromyography (EMG) data to ensure the activity or inactivity of muscles during the tasks. The use of EMG could have provided an explanation to our findings of bimanual reaching.

Finally, the object size and chair height were not scaled to variations in participants' body size. However, objects used during the reaching tasks were grip-sized and all participants easily reached and grasped with one hand successfully. Furthermore, all participants sat comfortably in our chair with their feet flat on the ground. With these instructions, we believe we reduced the possibility of cortical activations caused by any irrelevant movements.

Our findings support and extend the motor control literature by demonstrating that unilateral arm activity is driven by neuronal activation in the contralateral sensorimotor cortex, while bilateral activity (e.g. bimanual reaching and alternate stepping) is driven by bilateral sensorimotor cortex activation. Furthermore, the present study has shown the viability and sensitivity of fNIRS during dynamic and functional motor tasks. Overall, this study reinforces the feasibility of fNIRS in motor research, enabling future researchers to investigate the neural bases for motor control, learning, and development.

Figure 2.1. Objects used during a) unimanual raeaching and b) bimanual reaching.

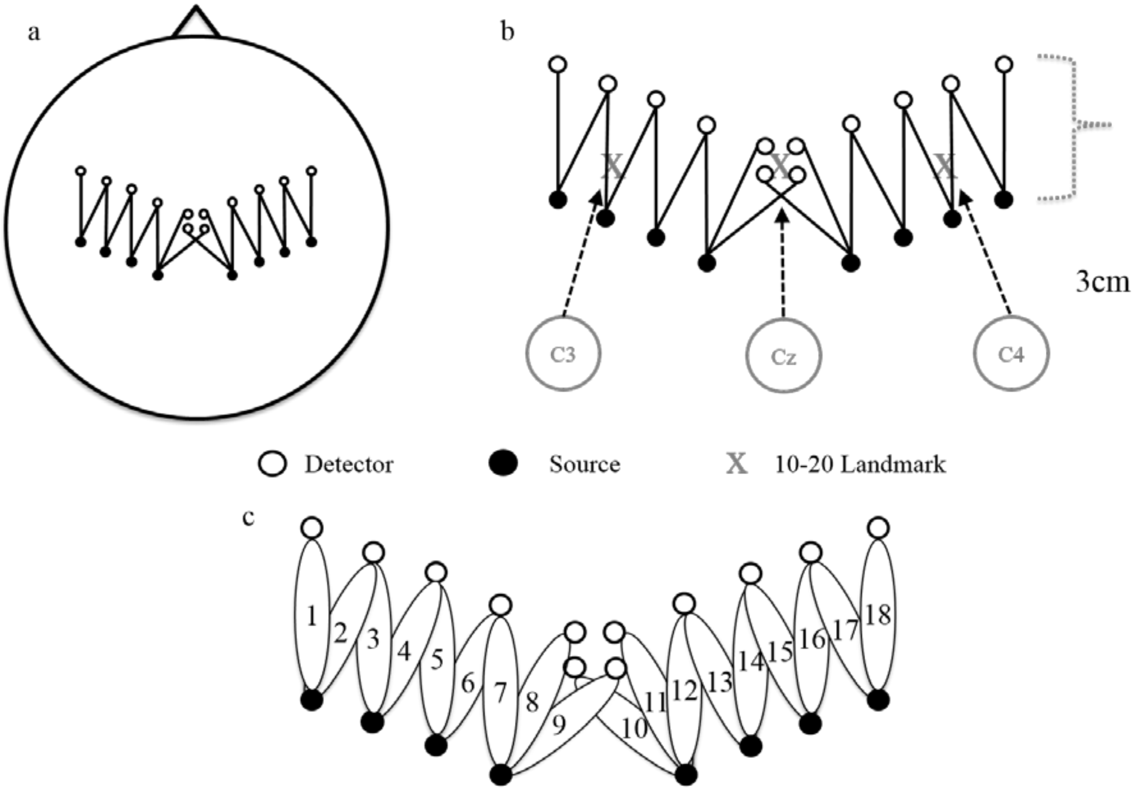

Figure 2.2. Probe configuration covering the bilateral primary motor cortex. In the upper left, a) shows a superior view of the orientation of the probe on the head; b) the position of the probe relative to the international 10-20 landmarks (the C3-Cz-C4 line); and c) the channel numbers.

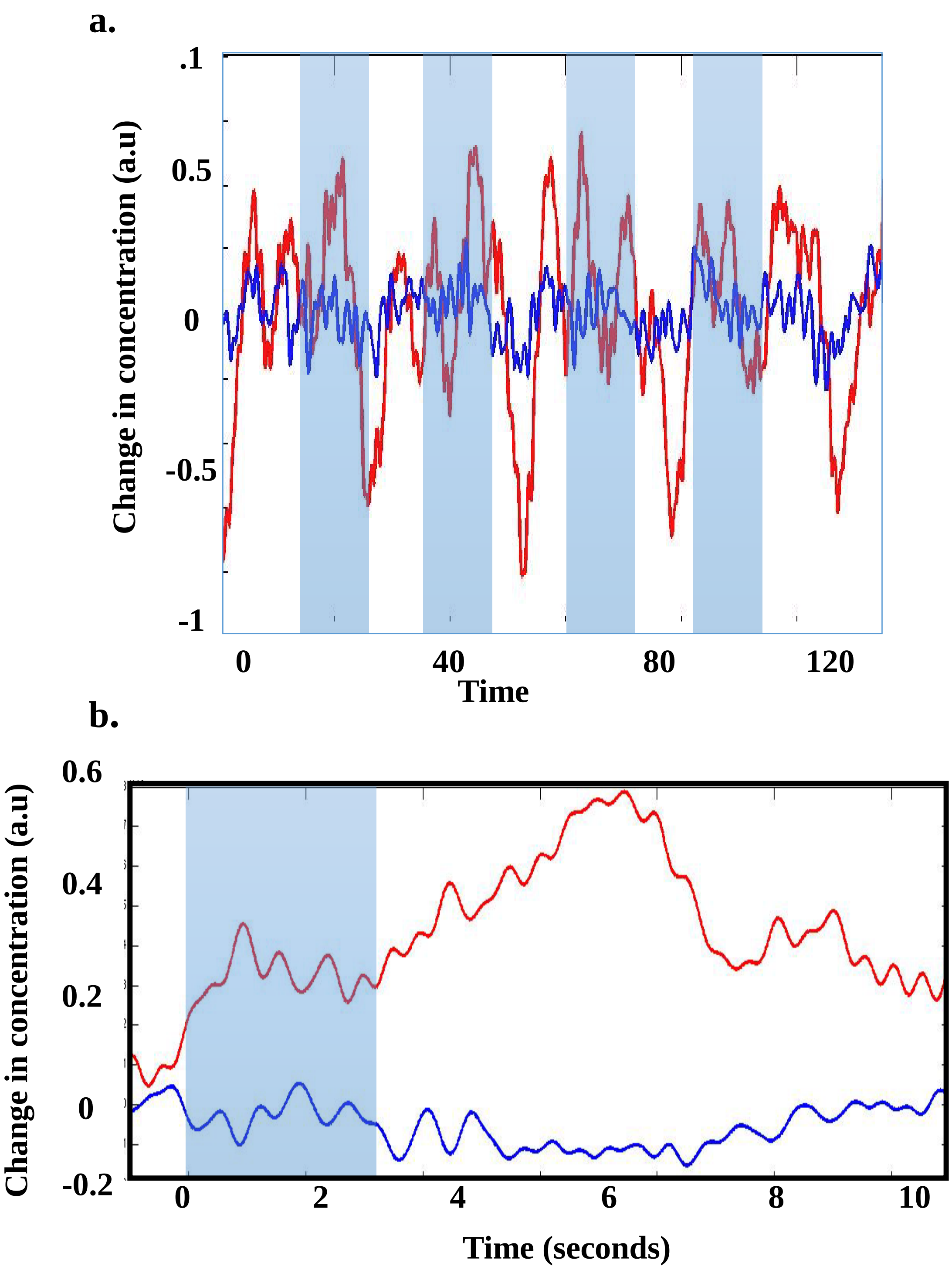

Figure 2.3. Exemplar data of active channel; a) preprocessed time series; b) average hemodynamic response function. Shaded regions indicate task phase.

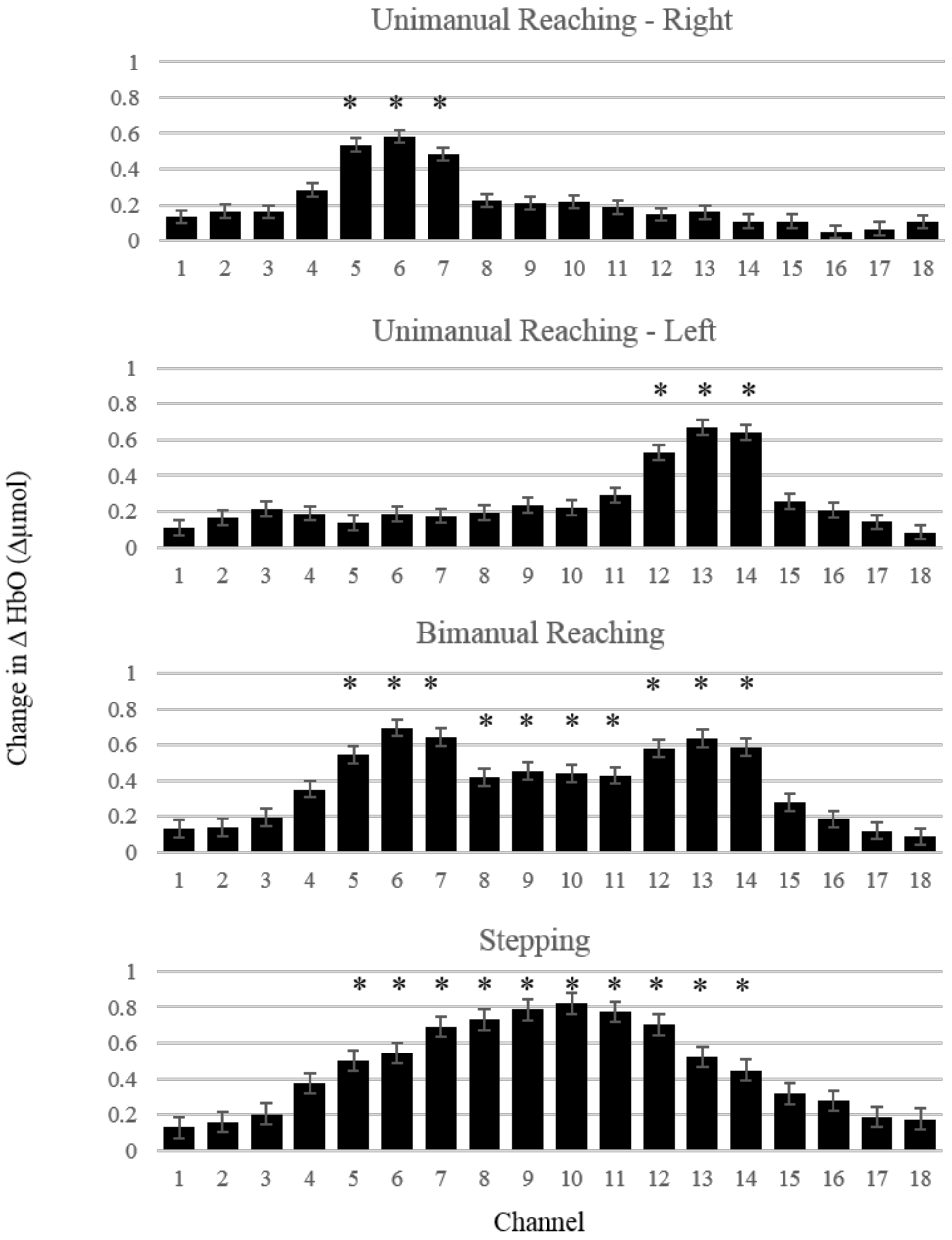

Figure 2.4. Group mean changes in HbO responses for each task relative to rest. Error bars represent SD. (* indicates statistically significant channels, $p < 0.05$).

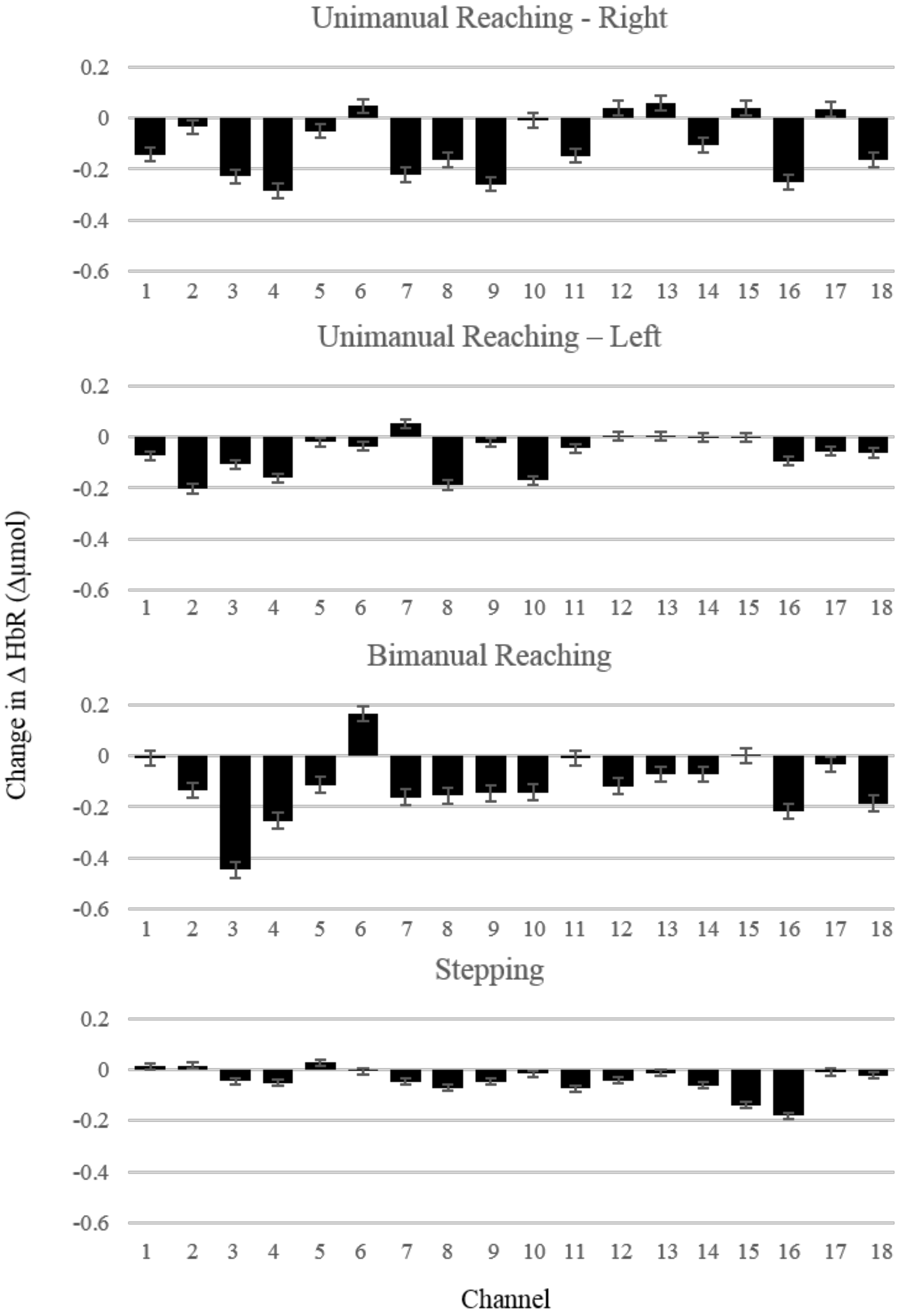

Figure 2.5. Group mean changes in HbR responses for each task relative to rest. Error bars represent SD.

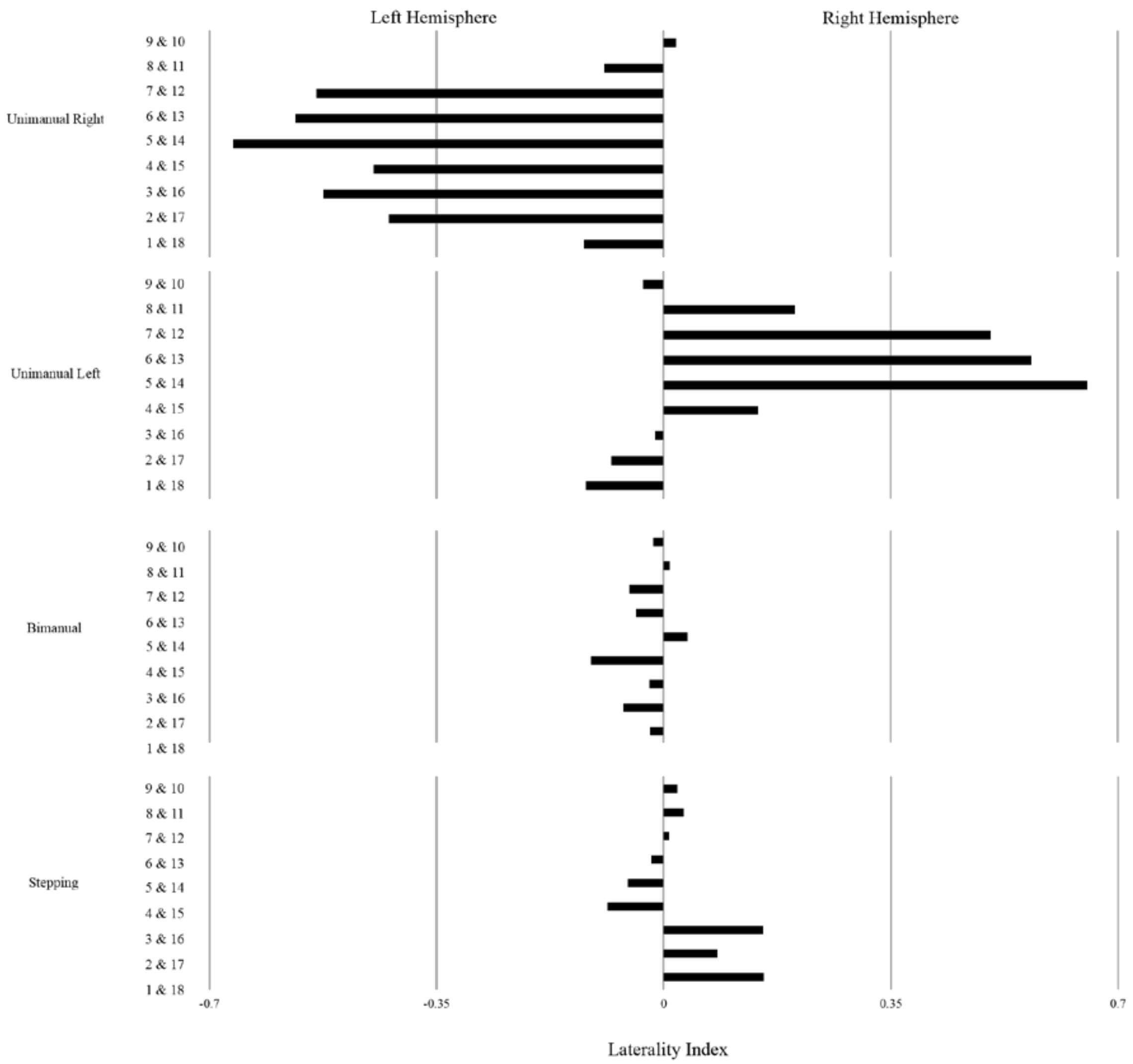

Figure 2.6 .Laterality index of mean oxygenation changes (HbO) for paired channels during each task. Negative values indicate the channel on the left hemisphere was higher than that of the right hemisphere channel.

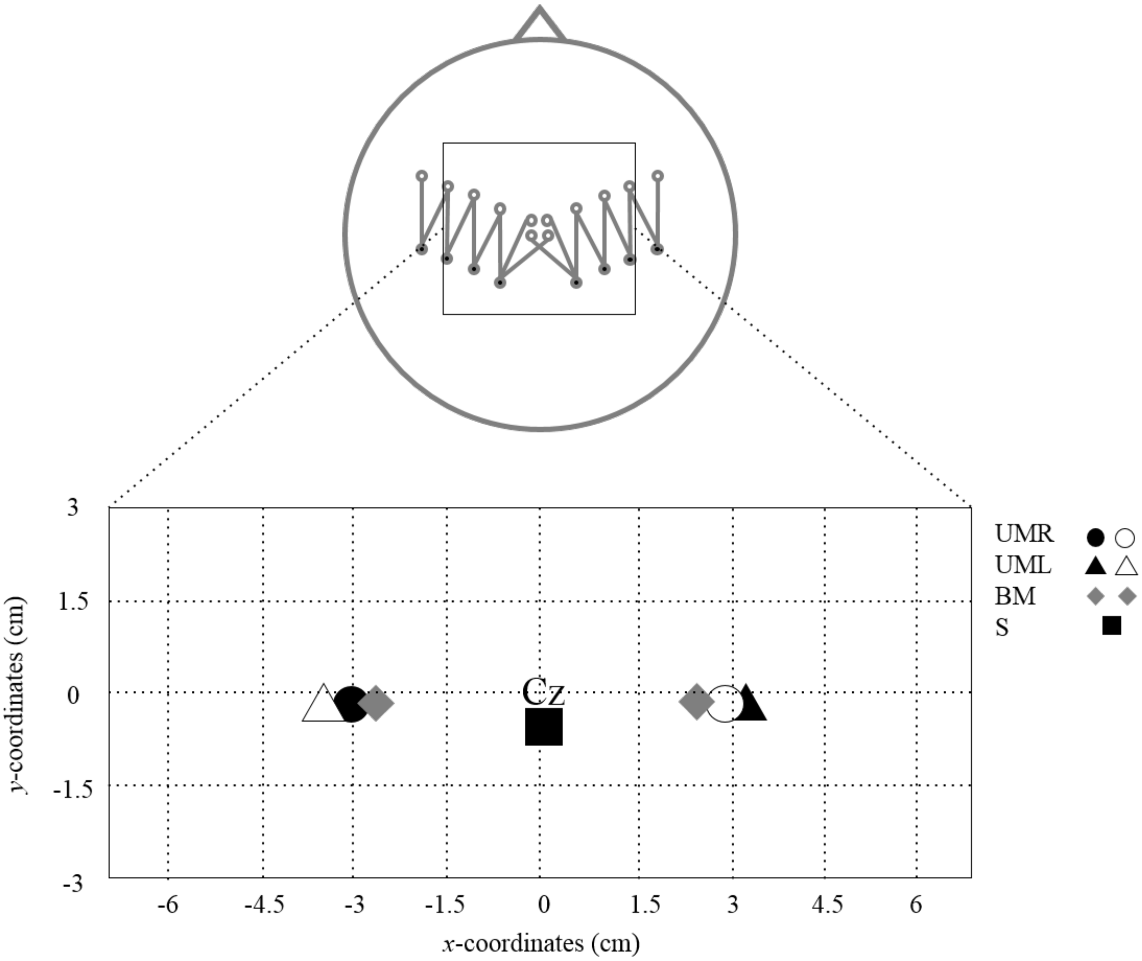

Figure 2.7. NIRS-CoGs of HbO for unimanual right (UMR), unimanual left (UML), bimanual (BM) and stepping (S). Filled markers represent contralateral and opened represent ipsilateral NIRS-CoG. Stepping NIRS-CoG was a single location.

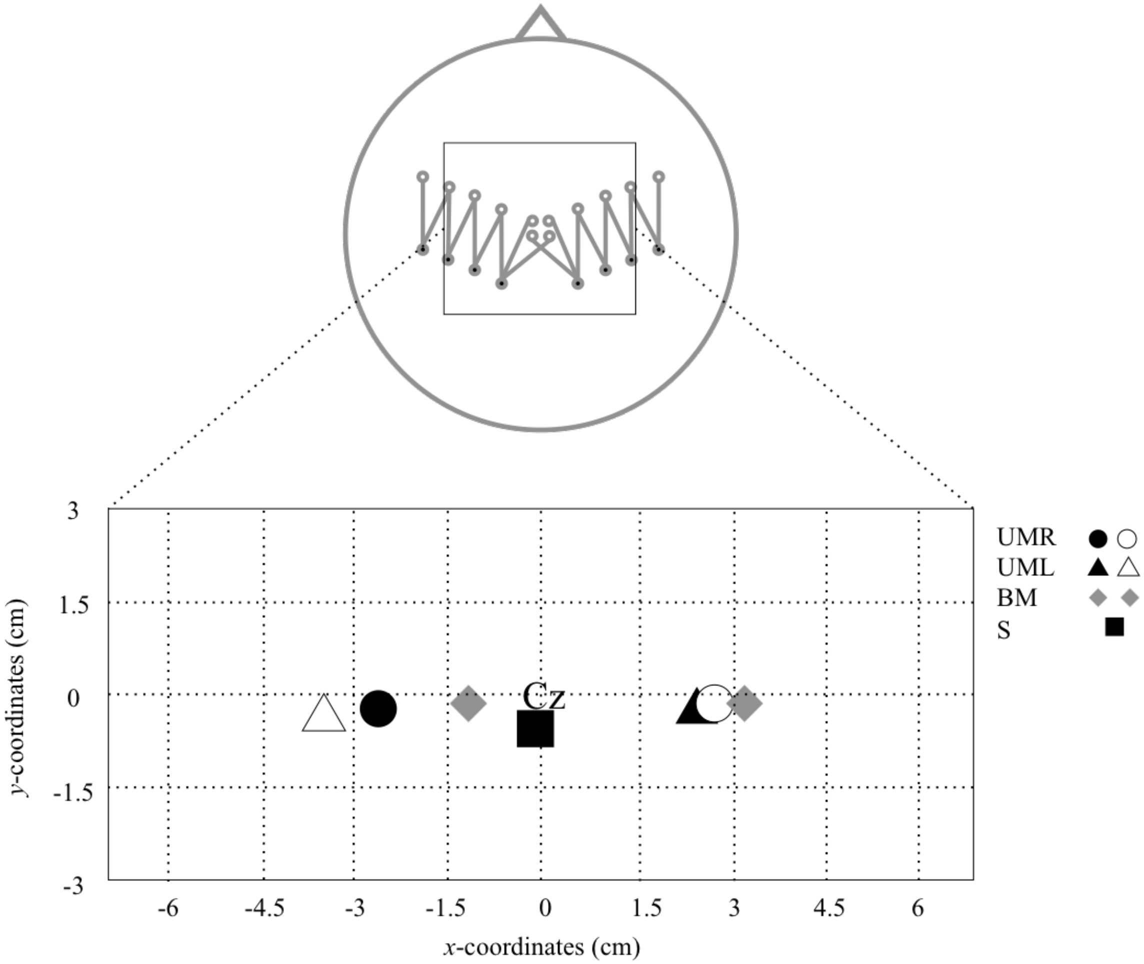

Figure 2.8. NIRS-CoGs of HbR for unimanual right (UMR), unimanual left (UML), bimanual (BM) and stepping (S). Filled markers represent contralateral and opened represent ipsilateral NIRS-CoG. Stepping NIRS-CoG was a single location.

Table 2.1. Summary of t-statistics for each task. * indicates p < .05.

Changes in HbO

Channel	UMR	UML	BM	S
1	-0.560	-1.898	-1.648	1.408
2	-1.366	-1.488	-1.704	1.656
3	0.054	-1.802	-1.164	1.135
4	-2.101	-1.492	-2.150	1.154
5	-2.388*	-1.528	-2.334*	1.361
6	-2.667*	-1.740	-3.560*	2.254*
7	-.2401*	-1.887	-2.319*	2.569*
8	-1.736	-2.138	-2.254*	2.334*
9	-1.112	-1.971	-2.256*	2.286*
10	-1.607	-1.822	-2.734*	2.300*
11	-1.579	-1.952	-3.531*	2.259*
12	-1.962	-2.307*	-3.985*	2.383*
13	-1.889	-2.380*	-4.176*	2.398*
14	-1.871	-2.270*	-3.024*	2.133*
15	-1.863	-1.768	-1.952	1.643
16	-1.319	-1.315	-1.799	1.632
17	-1.536	-1.319	-1.350	1.582
18	-1.713	-0.971	-0.932	1.118

Table 2.2. Summary of t-statistics for each task. * indicates p < .05.

Changes in HbR

Channel	**UMR**	**UML**	**BM**	**S**
1	-0.937	-0.515	-0.085	-0.592
2	-0.210	-1.535	-1.989	-0.578
3	-1.326	-1.150	-1.542	1.361
4	-1.594	-1.524	-1.643	1.757
5	-0.182	-0.191	-0.522	-0.807
6	0.280	-0.414	0.802	0.172
7	-1.520	0.297	-1.756	1.064
8	-1.908	-1.872	-1.048	1.489
9	-1.846	-0.231	-1.401	1.049
10	-0.122	-1.897	-1.392	0.414
11	-1.593	-0.474	-0.064	1.547
12	0.207	0.064	-0.958	0.942.
13	0.526	0.028	-0.497	0.205
14	-1.930	-0.021	-0.583	-1.395
15	0.907	-0.008	-0.015	-1.050
16	-1.335	-1.006	-1.687	-1.087
17	0.452	-0.563	-0.289	-0.106
18	-2.057	-0.537	-1.475	-0.735

Table 2.3. Mean responses from each channel across all tasks.

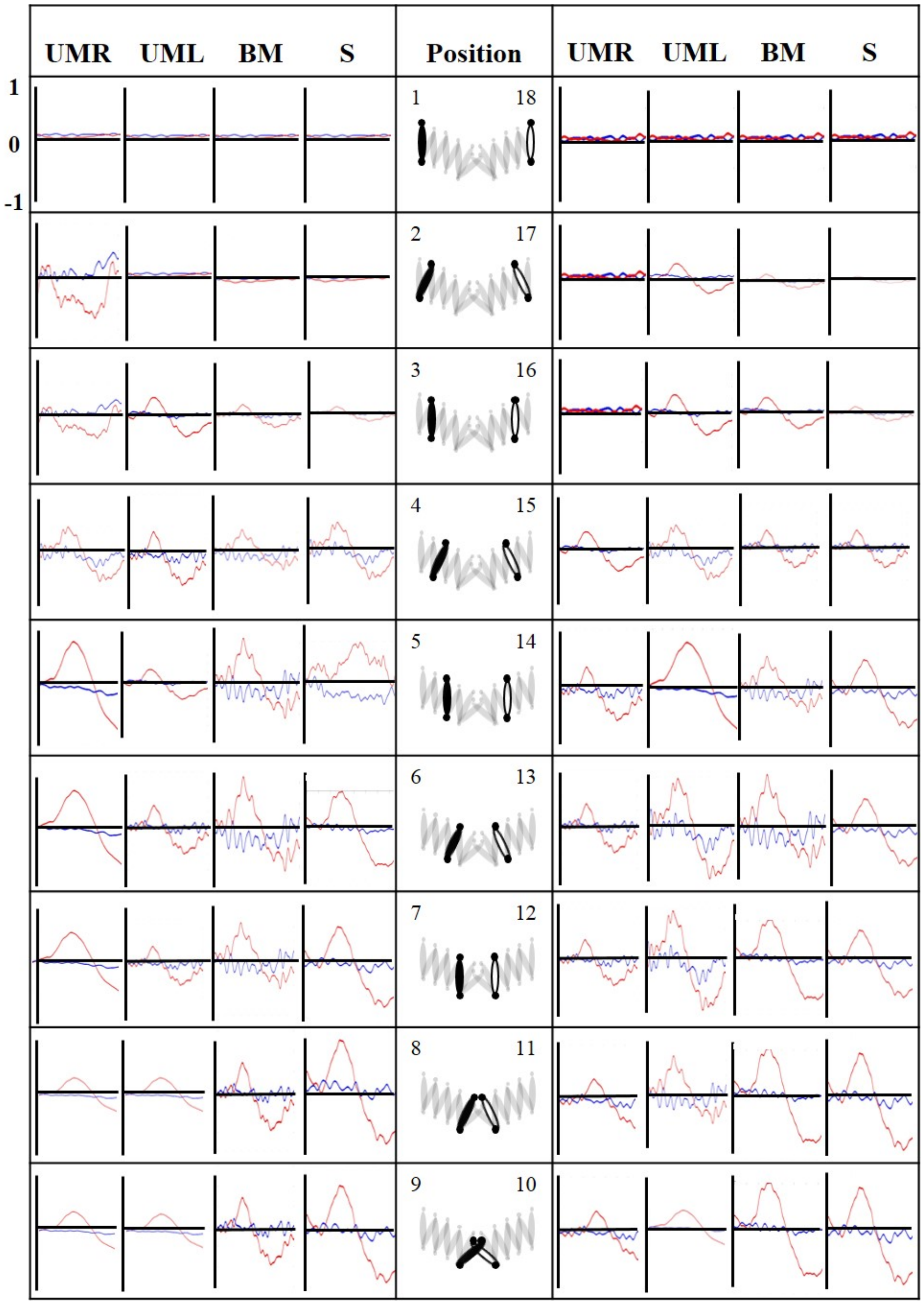

Table 2.4. Pairwise comparison of NIRS-CoGs for HbO in left (top) and right hemisphere (bottom). * indicates statistical significance ($p < 0.05$).

Left Hemisphere

	x-direction				*y*-direction			
	UMR Contra	**UML Ipsi**	**BM R-Arm**	**S**	**UMR Contra**	**UML Ipsi**	**BM R-Arm**	**S**
UMR Contra	-	.235	<.01*	< .01*	-	.392	<.01*	<.01*
UML Ipsi	.235	-	.005*	< .01*	.392	-	.006*	<.01*
BM R-Arm	<.01*	.005*	-	< .01*	<.01*	.006*	-	.687
S	< .01*	< .01*	< .01*	-	<.01 *	<.01*	.687	-

Right Hemisphere

	x-direction				*y*-direction			
	UMR Ipsi	**UML Contra**	**BM L-Arm**	**S**	**UMR Ipsi**	**UML Contra**	**BM L-Arm**	**S**
UMR Ipsi	-	.550	.436	< .01*	-	.346	.520	.093
UML Contra	.550	-	.029*	< .01*	.346	-	. 021*	< .01*
BM L-Arm	.436	.029*	-	< .01*	.520	.021*	-	.108
S	< .01*	. < .01*	. < .01*	-	.093	< .01*	.108	-

Table 2.5. Pairwise comparison of NIRS-CoG for HbR in left (top) and right hemisphere (bottom). * Indicates statistical significane ($p < 0.05$).

Left Hemisphere

	x-direction				*y*-direction			
	UMR Contra	**UML Ipsi**	**BM R-Arm**	**S**	**UMR Contra**	**UML Ipsi**	**BM R-Arm**	**S**
UMR Contra	-	.747	.619	.325	-	.276	.674	.907
UML Ipsi	.747	-	.445	.051	.276	-	.178	.132
BM R-Arm	.619	.445	-	.867	.674	.178	-	.691
S	.325	.051	.867	-	.907	.132	.691	-

Right Hemisphere

	x-direction				*y*-direction			
	UMR Ipsi	**UML Contra**	**BM L-Arm**	**S**	**UMR Ipsi**	**UML Contra**	**BM L-Arm**	**S**
UMR Ipsi	-	.772	.567	.325	-	.943	.346	.735
UML Contra	.772	-	.610	.155	.943	-	.680	.890
BM L-Arm	.567	.610	-	.867	.346	.680	-	.213
S	.325	.155	.867	-	.735	.890	.213	-

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Chapter III: Developmental Changes in Motor Cortex as Infants Develop Functional Motor Skills

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Abstract

Despite extensive research examining overt behavioral changes of motor skills in infants, the neural basis underlying the emergence of functional motor control has yet to be determined. We used functional near-infrared spectroscopy (fNIRS) to record hemodynamic activity of the primary motor cortex (M1) from 22 infants (11 six month-olds, 11 twelve month-olds) as they reached for an object, and stepped while supported over a treadmill. Based on the developmental systems framework, we hypothesized that as infants increased goal-directed experience, neural activity shifts from a diffused to focal pattern. Results showed that for reaching, younger infants showed diffuse areas of M1 activity that became focused by 12 months. For elicited stepping, younger infants produced much less M1 activity which shifted to diffuse activity by 12 months. Thus, the data suggest that as infants gain goal-directed experience, M1 activity emerges, initially showing a diffuse area of activity, becoming refined as the behavior stabilizes. Our data begin to document the cortical activity underlying early functional skill acquisition.

3.1 Introduction

Our ability to explore our surroundings by moving through space or reaching and manipulating objects allows us to acquire new information about our environment and is essential for human development and learning. But how do we develop these adaptive and complex skills? How do these skills, like reaching and walking, emerge and become stable?

Motor development researchers have constructed a body of evidence that describes the diversity, variability, and dynamic nature of motor skill acquisition particularly during infancy. To explain the bases for these behavioral outcomes, scientists have focused on studying the processes of change that drive these behaviors. With this goal researchers have investigated the relations among kinematic, kinetic, and overt functional changes of both successful and unsuccessful limb movements (Chang, Kubo, & Ulrich, 2009; Corbetta & Thelen, 1996; Teulier, Sansom, Muraszko, & Ulrich, 2012; Thelen et al., 1993; Thelen & Spencer, 1998). Efforts to interpret these relations based on current neuroscience and developmental theories, have led to hypotheses about the development of the central nervous system (CNS) and its role in the emergence of neuromotor control. Currently, however, we do not have direct evidence, or even descriptive evidence, relating brain activity with functional motor skills as they emerge. As a result, we have a knowledge gap in efforts to support or revise these hypothesized links between the brain and motor behaviors in infants. With the recent development of new infant‐friendly neuroimaging techniques, we can begin to construct a body of empirical evidence identifying the neural links to neuromotor control.

A set of overlapping theories, commonly referred to as dynamic systems theory (Thelen & Smith, 1994), developmental systems approach (Gottlieb, Wahlsten, & Lickliter, 1998), dynamic field theory (Wiebe, Morton, Buss, & Spencer, 2014), and interactive specialization (Johnson, 2001, 2011) all embrace and argue that new skills (patterns of behavior) are emergent, not prescribed. This framework posits that functional behaviors are outcomes of the interactions among multiple subsystems such as the nervous system, intrinsic body dynamics, environment, and the task or goal. New patterns are both discovered through exploration and stabilized through repetition or practice (Lewis, 2011; Smith & Thelen, 2003; Thelen & Smith, 1994; Ulrich & Ulrich 1993). Here, we will use the term developmental systems framework as the phrase and approach to effectively capture the essence of all aforementioned approaches. Infants must achieve a sufficient level of development of many components, such as postural control, motivation to achieve the goal, capacity to coordinate muscle activations, for new motor skills to emerge. But only with repetitions of the goal‐directed pattern, do stability and control follow. A growing body of empirical data regarding the changes in behavioral, kinetic, and kinematic patterns supports the developmental systems framework that explains the ontogeny of many new patterns of behavior such as reaching, stepping, and kicking (Corbetta & Thelen, 1996; Jensen, Thelen, Ulrich, Schneider, & Zernicke, 1995; Kanemaru, Watanabe, & Taga, 2012; Lockman & Thelen, 1993; Teulier, Lee, & Ulrich, 2015; Thelen, 1995; Thelen et al., 1993; Thelen, Corbetta, & Spencer, 1996; Watanabe, Homae, & Taga, 2010). Yet, there is very limited empirical evidence regarding neural basis that underlies the emergence of new patterns of behavior, specifically with functional motor skills.

Theories focused on how the brain becomes organized to control functional behavior compliment the developmental systems approach; particularly relevant are Edelman's theory of neuronal group selection (TNGS, Edelman, 1987; Sporns & Edelman, 1993) and dynamic neural field theory led by Gregor Schöner, Kopecz, and Erlhagen (1997). Both theories link behavior and the neural dynamics as co-evolving over time (Samuelson, Jenkins, & Spencer, 2015; Sporns & Edelman, 1993). Specifically, TNGS proposes that early in skill acquisition, there is a particularly high redundancy in the nervous system. This redundancy is manifested in the intrinsic overproduction of unspecified neurons and synaptic connections and facilitates discovery of ecologically meaningful goals (Bertenthal & Campos, 1987; Greenough, Black, & Wallace, 1987). Selection drives much of neural organization, that is, as infants identify a goal and attempt to achieve it, such as to reach for an object they see or move their bodies through space, they activate neural circuits in multiple relevant areas of their brains. For example, over time and much practice, as seen in adults, the primary motor cortex becomes functionally and topographically specialized, activating efficiently muscles used to perform voluntary movements (Halsband & Lange, 2006; Muellbacher et al., 2002; Nishiyori, Bisconti,& Ulrich, 2015). Early in skill acquisition, however, large and diverse areas of neurons would be active as movement options are explored. As the movement outcomes become more reliable, neural activity in parallel would become more focal and efficient, gradually evolving into the topographic organization seen in adults. Thus, we must begin to determine the neural activation patterns during early skill acquisition in infants.

Our goal here was to begin to describe the early activation of motor cortex neurons as infants acquire skills. We chose two well-studied functional motor skills in infants: reaching for a toy with the upper limbs and the production of stepping patterns with the legs while supported upright on a treadmill. Reaching is an important functional skill that emerges during the first 6 months after birth. For reaching to emerge, theorists argue that infants must be able to visually locate the target, control the muscles of the arms, and control their posture and head (Clearfield & Thelen, 2001). Moreover, we know that young infants show variable patterns of movement as they attempt to obtain a toy; and as they gain more experience moving their arms and attempting to reach their goals, their movement become smoother, reliable, accurate, and muscle activation patterns become more efficient (Thelen et al., 1993, 1996). That multiple subsystems converge and patterns of movement become stable as infants gain experience through repeated cycles of action and perception has been established by behavioral studies. That is, as infants make repeated attempts to reach for objects, they fine-tune their actions with the environment as stable patterns of movement form (Corbetta & Bojczyk, 2002; Corbetta & Snapp-Childs, 2009; Williams, Corbetta, & Guan, 2015).

Later in the first year, infants experience similar cycles, but with their lower limbs as they begin to engage in upright leg activity. Functional control over the legs, unlike the arms, does not emerge until the second half of the first year. While step-like patterns, such as newborn stepping, can be elicited from birth to approximately 6–8 weeks, voluntary stepping in the form of cruising (walking with support) and walking (independently) emerge between 9 and 12 months. Thelen and colleagues, used a series of studies to illustrate the dynamic confluence of many subsystems over time in this developmental trajectory of the production of infant stepping patterns. They documented, for example, that when newborn stepping "disappeared" in the upright posture, similar lower-limb kinematics persisted in other contexts: when supine, infants kicked and when legs were submerged in water, they stepped (Thelen, Fisher, & Ridley-Johnson, 1984, Thelen, Fisher, & Ridley-Johnson, 2002; Thelen & Fisher, 1982). Furthermore, across the first year post-birth, when supported over a treadmill, researchers could elicit from infants alternating stepping patterns, though infants also displayed multiple inter-limb coordination patterns (Thelen, 1986; Thelen & Ulrich, 1991; Ulrich, Jensen, & Thelen, 1991). Thus, the adaptive and changing nature of stepping behaviors, like other behaviors, demonstrate that the subsystems available to produce body segment trajectories including factors external to the infant are softly assembled and can affect the presence or absence of any particular overt behaviors across time. Based on the behavioral data amassed thus far and theories about the development of the CNS, the next logical step in explaining early skill acquisition would then be to examine more directly infants' brain activation patterns as they begin to improve their control of their limbs during essential basic skills, such as reaching and stepping.

Mapping developmental systems framework principles to real (as opposed to modeled) brain activity during the acquisition or performance of functional motor skills in infants has been limited to date by the constraints of traditional neuroimaging techniques. For example, when using functional magnetic resonance imaging (fMRI) the head must be stationary and the machine is loud (Almli, Rivkin, & McKinstry, 2007). Event‐related potentials (ERPs) obtained through electroencephalography (EEG) are quiet and less head stabilization is required, but still experience high attrition rates due to the dynamic nature of the stimuli which causes infants to move (Stets, Stahl, & Reid, 2012), introducing movement-related artifacts.

Recently, technological advances in the use of functional near-infrared spectroscopy (fNIRS) have enhanced its effectiveness in brain-imaging studies focused on developmental questions (Lloyd-Fox, Blasi, & Elwell, 2010; Vanderwert & Nelson, 2014). fNIRS utilizes source optodes that emit near-infrared light which is projected through the scalp, skull and the cerebral cortex, then reflected back out of the brain and picked up by detector optodes. Changes in the reflected light intensity occur as concentrations of oxygenated (HbO) and deoxygenated (HbR) hemoglobin vary, which arise due to activation of the sampled brain tissue (Villringer & Chance, 1997). fNIRS technology offers a number of advantages over fMRI and EEG. fNIRS has a greater spatial resolution compared to EEG and the temporal resolution of fNIRS is greater than that of fMRI (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006). This system is more resilient to movement‐related artifacts than fMRI and EEG and is not subject to rigid head stabilization or supine posture of fMRI. Most important for our questions is that fNIRS allows participants to assume a naturalistic posture specific to a movement task while tolerating larger limb movements. (Lloyd‐Fox et al., 2010; Quaresima, Bisconti, & Ferrari, 2012; Vanderwert & Nelson, 2014).

Brain imaging studies of children and adults show that the primary motor cortex activates the muscles to produce voluntary goal-directed movements and plays a role in practicing and consolidating new skills (Filimon, Nelson, Hagler, & Sereno, 2007; Indovina & Sanes, 2001; Koenraadt, Duysens, Smeenk, & Keijsers, 2012; Koenraadt, Duysens, Meddeler, & Keijsers, 2013; Nishiyori et al., 2015). These neural excitation patterns have not been tested or observed in human infants, that is, their origins are not known. Skills used in motor studies for adults involve learning a new sequence or adapting to a new constraint during a repeated goal, such as to manually control a joy‐stick correcting for a force perturbation; the basic movements themselves, however, have been extensively practiced and used for years prior. Thus, we do not have direct developmental data to illustrate: (i) how the primary motor cortex becomes organized in the way we observe it to be in adults; (ii) the level of activity in the primary motor cortex when skills that are truly novel and nascent are attempted; and (iii) how primary motor cortex activation patterns change as skills improve over time. The specific goals of our current study were to delineate the developmental changes in brain activity for two distinctly different tasks: reaching for a toy with the upper limbs while seated, and stepping with the legs while supported upright on a treadmill. Reaching represents a functional, voluntary, and self-initiated skill with a clear goal which infants produce successfully by about 4 months of age and subsequently practice many times daily. In contrast, stepping while supported over a treadmill is an elicited movement pattern with recognizable limb patterns. Infants never practiced treadmill stepping; at 6 months they have not begun to step voluntarily but by 12 months most have, at least begun to practice stepping as they start to cruise. Here, we explored the emergent patterns of motor cortex activity associated with infants' motor patterns, at two developmental time points, 6 and 12 months. At 6 months of age, infants had 1-2 months of practice reaching for toys, but minimal to no experience stepping upright or cruising. By 12 months of age, infants are very skillful reachers but are relative novices at voluntary stepping (1-2 months of gaining upright posture and cruising or walking). Based on the developmental systems framework and previous developmental neuroscience data, we proposed that the motor cortex neural activation change as infants discover patterns that fit their self-selected goals and then repeat cycles of practice (e.g., creating and enhancing the perception-action links) to accomplish these goals. More specifically, we hypothesized that with increased goal-directed experience, brain activity will shift from diffuse to more refined and focal activity. That is, 6 month-old infants will exhibit a dispersed area of motor cortex activity (nascent reaching) compared to 12 month-old infants during reaching when the skill is well established. During stepping, 6 month-old infants will exhibit reduced areas of cortical activity because it is not voluntary or “goal-directed”, compared to 12-month old infants, who will show a dispersed area of motor cortex activity because they are nascent “walkers,” similar to the 6 month-old brain activity during reaching.

3.2 Method

3.2.1 Participants

We consented 34 infants, 14 in the younger and 20 in the older age groups. Of these, one of the younger infants and three of the older infants became too fussy during preparation for testing to allow us to collect data. In addition, two of the younger infants and three of the older infants’ data were unusable due to extensive noise, motion artifacts, or too few usable channels. This resulted in 11 of the younger infants and 14 of the older infants for whom we had usable data for reaching and/or, stepping. Not all infants’ data were usable from both tasks, thus the final numbers, ages, and gender for each task and age group were: reaching = 11 younger (M= 26.12weeks, range = 23.2–29.9 weeks, seven females) and 11 older (M= 52.2 weeks, range = 50–56 weeks, seven females); stepping = 11 younger (M= 26.12 weeks, range = 23.3–29.9 weeks, seven females) and 11 older (M= 52.1weeks, range = 49.3–56.6 weeks, six females) infants. Table 3.1 presents a summary of the participants’ characteristics.

3.2.2 Session Overview

Upon arrival to the lab, we allowed infants to acclimate to our space and interact with the research team. During this time, a research team member explained the study to parents and answered any questions with the parents, who read and signed the informed consent. Next, we removed infant's clothing except their shirt and diaper to allow infants to move freely. We measured the infant's head circumference, distance between inion and nasion, and left pre-auricular to right pre-auricular point to identify the vertex of the head, or Cz according to the 10‑20 international system (Jasper, 1958). After we placed the infant into the customized infant seat, we secured the headgear on the infant's head. Floor to ceiling curtains were approximately 60 cm away from both sides of the table on which the infant seat rested, which minimized the amount of distraction due to open space. We began testing with the reaching task, followed by a brief break and then tested the stepping task. During the break, we re-arranged the lab to prepare for the stepping task. After completion of the stepping task, we took photographs of the headgear on the infants to ensure the optodes/headgear had not moved from the target areas, as this could affect the quality and precision of our fNIRS measurements. We then removed the headgear and took basic anthropometric measurements (e.g., weight, total body length, leg length and circumference, and thigh and umbilicus skinfold). Finally, we administered the Motor Subscale of the Bayley Scales of Infant Development III (BSID-III, Bayley, 2006).

3.2.3 Tasks

3.2.3.1 Reaching

For the reaching task, infants were secured in a customized infant seat (seat pan was 32 cm above the table top, backrest: 75 cm long, and reclined approximately 10° from the vertical) with a chest strap. The infant seat was secured on top of a table [117.4 (L), 59.5 (W), 79.5 cm (H)], so that infant's head would be at eye level with the video monitor.

We positioned a video monitor (23” LCD, Phillips, Andover, MA, USA) on a cart in front of and approximately 80 cm away from the seat. We hung a thick black curtain in front of the monitor that could be opened and closed to hide the monitor during reaching trials and revealed videos playing during the rest phase (Figure 3.1). For reaching trials, a variety of age-appropriate small grip-sized toys [5 (L) × 5 (W) × 5 cm (H), Figure 3.2] were presented to elicit reaching and maintain interest.

For the task phase, an experimenter presented the toy at the infant's midline within reach, followed by a rest phase. The experimenter first retrieved the toy from the infant then unveil the monitor playing an infant entertainment video (e.g., Baby Einstein) intended to keep the infant calm and still for a minimum of 20 s (rest phase). If after 10 s from toy presentation, the infant did not reach for the toy we presented, we began a rest phase then started a new trial with a new toy. We repeated the cycle of reaching and rest for a minimum of 10 successful trials.

3.2.3.2 Stepping

We placed our custom‐designed treadmill [frame: 93.5 (L) × 43.7 (W) × 21 cm (H); belt: 81.5 (L) × 30.6 cm (W)] on top of and near the front edge of the same table used for reaching, in the center of the room (Figure 3.3). Each trial consisted of a rest‐phase followed by a stepping phase. We started with a 30 s rest phase. During the rest phase, the experimenter held the infant who rested against the experimenter's chest. From pilot sessions, we determined that this was the best position to keep the infant calm and minimize movements thus optimizing rest phase status and values. Following the rest phase, each stepping phase lasted 30 s. During the stepping phase, an experimenter supported the infant under the arms so they were upright with feet touching the belt surface. Infants were encouraged to support as much of their weight as they could; experimenter provided supplemental weight support and posture control. The treadmill belt speed was set at .20 m/s for both younger and older infants based on previous research which showed this to be the most effective speed to elicit alternating steps in infants across the first year of life (Teulier et al., 2009). If infants did not respond to the moving belt with any leg movements during a trial, that is they allowed their legs to drag and extend behind them, we lifted the infant up to bring their legs forward and placed them on the belt again to encourage a motor response - stepping. We collected a minimum of 10 successful stepping trials.

3.2.4 fNIRS Data Acquisition

To record the hemodynamic responses of the primary motor cortex (M1) during reaching and stepping tasks, we used a continuous wave fNIRS system (CW6; TechEn Inc., Milford, MA) which utilized two wavelengths (690 and 830 nm) and sampled at 50 Hz. Near-infrared light was delivered via fiber optic cables that terminated into customized headgear (Figure 3.4). The base of the headgear was an adjustable headband (Velcro, Manchester, NH, USA) with a panel with extensions, both made of blue Dycem. In this panel, we embedded the base for the optodes (grommets, TechEn, Inc., Milford, MA, USA). The fNIRS cables/optodes were connected to the panel prior to placing the apparatus on the infant's head. Extensions of this panel connected to the headband, which allowed us to adjust a snug fit for each infant. The headgear contained four source- and six detector-optodes placed approximately 2.5 cm apart creating a 12-channel array. We positioned the headgear on the infant's head in alignment with Cz as defined by the 10‑20 International system (Jasper, 1958). Channels covered the area around the C3 and C4 landmarks, thus our configuration placed the optodes in position over theM1or Brodmann Area (BA) 4 (Figure 3.4). The design of our probe array was based on a study we completed previously with adults (Nishiyori et al., 2016).

3.2.5 Video Recording

We used a digital camcorder (Canon, Melville, NY, USA) that sampled at 60 Hz to record both reaching and stepping tasks. During the reaching trials, the video was mounted on a tripod positioned at a 45° from midline and 100 cm away from the center of the infant seat. During stepping trials, the camcorder was repositioned perpendicular to the side of the treadmill. In these positions, we were able to identify the activity of all four limbs and the trunk. Furthermore, these views allowed us to view any gross movements of the headgear and fNIRS cables. The onset of task, rest phases, and any undesired behaviors such as crying and head turning were documented. The camcorder and fNIRS system were synchronized via an audio signal. At the start of each condition, we inserted an audio signal simultaneously to the video and fNIRS data. We then mapped the timing of the onset of reaches and steps and the start of the rest phases onto the fNIRS data to identify functional movement-related changes in hemodynamic activity of M1.

3.2.6 Bayley Scale of Infant Development – Motor Subscale

At the end of the session, we administered the Motor Subscale of the Bayley Scales of Infant Development (BSID ‐ III). This scale allowed us to characterize the status of gross and fine motor skill acquisition between the two groups.

3.2.7 Trial Rejection

To determine the usability of trials, all videos were behavior coded offline by two different researchers. For reaching, trials were valid if the infant reached for and successfully grasped the object. Trials were not considered for further analysis if infants did not reach for the object. For stepping, trials were valid if the infant stepped in response to the moving belt. Trials were not considered for further analysis if infants did not step in response to the moving belt. For instance, if the infant allowed her legs to drag behind them for a majority of the trial, we did not code this as a stepping trial.

3.2.8 fNIRS Data Processing

fNIRS data were processed using the Homer2 (Huppert, Diamond, Franceschini,&Boas,2009)Matlab toolbox (Mathworks,MA). Data were low-pass filtered at .8 Hz and then motion-corrected using a wavelet-based filtering (Molavi & Dumont, 2012). The optical density signal was then converted into concentration using the modified Beer–Lambert Law. Partial path-length factor was set at 6.0 and the known coefficients of oxygenated (HbO) and deoxygenated (HbR) hemoglobin (Cope et al., 1988; Obrig & Villringer, 2003). Concentration data were then time locked to movement onset and epoched. For the reaching task the epoch consisted of 3 s prior to and 10 s post onset of reach. For the stepping task, the epoch was 1 s prior to and 10 s post onset of stepping. Epochs were averaged for each channel, group, and task and baseline corrected to pre-movement period. Outlier trials in which task-related change in HbO and HbR exceeded two standard deviations were excluded from further analysis. With this criterion, 16% of the total 440 test trials (11 participants × two groups × two tasks × 10 trials = 440 test trials) were excluded. Finally, six brain regions of interest (ROIs, Figure 3.4) were then defined for analysis by pairing adjacent anterior and posterior channels.

3.2.9 Data Analysis

Three dependent variables of interest were extracted from the data. First, in order to determine the number of functionally active ROIs, the change in HbO values from each ROI within the epoch were used. We used an independent samples t-test to detect any significant changes between pre- and post-onset of the movement for all trials. This test provided the number of ROIs demonstrating task-related activity, which were then compared across group for each task using separate independent t-tests. The dependent variable of number of active ROIs was quantified as a tally of significant ROIs for each infant in each task. The same analysis was performed for HbR. Second, percent signal change were calculated based on the change of concentrations for both HbO and HbR compared to rest values within an epoch. We then determined group differences in peak activity by comparing percent signal change in the ROI demonstrating peak HbO change from each participant. Separate independent samples t-tests were performed for reaching and stepping. Finally, we summed the percent signal change of the active ROIs to calculate the volume of activity during a task. The volume of each HbO (sum of percent signal change across active ROIs) across groups was compared for each task using separate independent samples t-tests for each task. Volume derived in the manner provides an indication of percent signal change across significant ROIs. In conjunction with the number of active ROIs and peak signal change, it can provide information about the focality of cortical activity that neither the number nor peak signal change alone can provide.

3.3 Results

3.3.1 Motor subscale of the Bayley scales of infant development

The Bayley data, revealed that younger infants, as expected, achieved fewer items, 47, than older infants, 74 items. The scores were tightly clustered for each age group, therefore we could not make meaningful comparisons with the fNIRS data.

3.3.2 Reaching

An average of 10.4 (SD = 2.1) and 11.0 (SD = 3.0) reaching trials were considered valid and included in the data analysis for younger and older groups, respectively.

The independent samples t-test on the number of active ROIs for HbO during reaching revealed that younger infants (5.1 ± .25 ROIs) showed significant activity in a larger number of ROIs compared to older infants (2.7 ± .38 ROIs, *t*(10) = 5.221, P < .01). There were no differences across groups in the number of ROIs demonstrating significant change in HbR (Younger = 1.09 ± .21 ROIs, Older = .64 ± .15 ROIs, *t*(10) = .65, P = .27). Despite differences in the number of ROIs for HbO, the percent signal change in HbO for the peak ROI was not different between younger (.72 ± .20 μM) and older infants (.72

± .08 µM, *t*(10) = .21, P = .98). A comparison of the volume of activity revealed that younger infants (.32 ± .25 µM) demonstrated lower volumes of activity compared to older infants (1.37 ± .24 µM, *t*(10) = 2.531, P = .03). Overall, while percent signal change was similar at the peak ROI, younger infants tended to demonstrate lower levels of reaching related activity distributed across a larger number of ROIs compared to older infants (Figures 3.5 and 3.6).

3.3.3 Stepping

An average of 8.8 (SD = 2.6) and 7.2 (SD = 2.7) stepping trials were considered valid and included in the data analysis for younger and older groups, respectively. These trials consisted of bouts of alternating steps. Trials in which infants dragged their feet or did not respond with leg movements, were not included in this analysis.

In contrast to reaching, during stepping younger infants (2.6 ± .15 ROIs) demonstrated fewer ROIs showing significant HbO change compared to older infants (3.5 ± .24 ROIs, *t*(10) = 3.1, *p* = .01). There were no differences between groups in the number of ROIs demonstrating significant change in HbR (Younger = 1.73 ± .24, Older = 2.28 ± .33 ROIs, *t*(10) = .21, *p* = .42). While older infants demonstrated a greater number of active ROIs during stepping, activity in the peak ROI was significantly lower or younger infants (.30 ± .05 µM) compared to older infants (.84 ± .17 µM, *t*(10) = 2.78, = .02). A comparison of the volume of activity across group revealed that younger infants (.59 ± .13 µM) demonstrated lower levels of activity across all active ROIs compared to older infants (1.8 ± .45 μM, *t*(10) = 2.37, P = .04). Overall, motor cortex activity was lower across all three measures in younger infants compared to older infants during stepping (Figures 3.5 and 3.6). Summary of the number of active ROIs can be found in Table 3.2 (HbO) and Table 3.3 (HbR).

3.4 Discussion

The goal of our current study was to take the first step in identifying the emergent patterns of cortical activation in infants as they produce and practice early motor patterns. We hypothesized, based on the developmental systems approach (Gottlieb, Wahlsten, & Lickliter, 1998) and TNGS (Edelman, 1987; Sporns & Edelman, 1993) that as infants explore and perform repeatedly, goal-directed actions, such as reaching for an object or moving their bodies through space, they activate large numbers of redundant neural circuits. Therefore, we predicted larger areas of activity in the primary motor cortex during early attempts leading to smaller areas of activity as skills improved. Results of our present study supported these predictions, particularly true when infants demonstrate clear goal-directed efforts. More broadly and consistently, our results demonstrated significant changes in activation patterns, that is, the dynamic nature of cortical activation, across ages and tasks. Together, these data suggest that neural responses underlying motor outcomes are associated with both the specific motor goal and experience pursuing it.

3.4.1 Motor Cortex Activation During Reaching

Both younger and older infants showed similar amplitudes in peak activity at their respective ROIs with the largest change in concentration. However, younger infants demonstrated activity across a wider area of the cortex compared to older infants, as indexed by the number of ROIs activated. Further, the broader cortical activity is characterized by smaller task-related activity, as indexed by the volume of activity. This pattern of results is consistent with less refined neural activity during skilled reaching. Reaching is functional but not fully stable by 6 months of age. At this age, there is coactivation of muscle activity when infants reach for an object in a similar setup to ours (Thelen et al., 1993). This means that younger infants recruit increased resources (e.g., area), explained by their necessity for postural control, in addition to coactivating more muscles than needed to reach for an object. Interestingly however, younger infants had comparable peak activity to older infants. Younger infants are able to drive the target muscles to reach but also activate other muscles (coactivation) that they have not learned to inhibit or control. As reaching skill develops towards 12 months of age, it appears that development is characterized by refined movement patterns rather than increased activity of task-relevant motor cortical representations. This is captured by previous reports of improved postural control, kinematics and dynamics in 12 month olds (Dusing, Thacker, Stergiou, & Galloway, 2013; Konczak, Borutta, Topka, & Dichgans, 1995; Thelen & Spencer, 1998) as well as the more focal activity in M1 observed here.

3.4.2 Motor Cortex Activation During Stepping

During stepping, younger infants activated a smaller area of motor cortex activity with both a lower peak and lower volume of activity compared to those of older infants. Stepping is an unexplored behavior for infants at 6 months of age, and is only observed when we create this unique context of supporting them over a moving belt. They were only able to achieve the stepping behavior at this age because we provided them with postural and body weight support.

Findings from animal studies show that higher brain centers, such as the cerebral cortex, are vital for the initiation of walking and to balance and support one's weight, but the alternative activations of muscles when supported on a treadmill to produce stepping patterns is controlled at the spinal level. Cortical contributions also appear to be integral for the modulation of gait patterns, for example in obstacle avoidance (Drew, Prentice, & Schepens, 2004). Therefore, stepping at this point in development, may not elicit significant or unique motor cortex activity during treadmill stepping in the absence of a volitional context or at least practice. More specifically, 6 month olds have not yet developed the volitional will to walk or step, especially in our context of treadmill stepping, in which the goal is not clear. By 12 months of age, our infants when stepping, showed the kind of diffused activity in the motor cortex that we observed for 6 month-olds as they reached. At this age, infants have had 1-2 months of experience being upright as well as a practice producing volitional goal-directed behavior like cruising along furniture, and many have taken their first independent steps. Thus, compared to younger infants, these older infants understand the requirements to maintain their balance when the belt moves their legs from under them, which they accomplish by initiating continuous and alternating steps. Older infants activate a diffused area of the M1 to drive the activation of muscles to voluntarily step on the treadmill. We hypothesize that, much like in reaching, continued experience with walking would result in refinement of the motor cortical activity observed at 12 months. There is an alternative explanation that must be considered, one that could potentially reflect a maturationist approach to the nature of stepping. That is, when younger infants stepped when we supported them on the moving belt of the treadmill, the neural drivers are those predesigned neuronal step pattern generators located in the spinal cord and not neurons located in the primary motor cortex. At this point in time, maturation of the higher brain centers should inhibit this spinal reflexive activation (Forssberg, 1985; Lamb & Yang, 2000). However, while this strictly maturational approach would argue the brain should inhibit the spinal activity, the fact is infants are moving their legs in patterns we categorize as stepping. Perhaps the richness of the supported treadmill context (researcher providing postural support and balance, movement of the treadmill belt stretching muscles and joints and the gravity assisting with swing phase and momentum carrying the leg forward in a step) overcomes the inhibitory tendencies of the higher brain centers. Clearly, by the end of the first year, both theoretical approaches, maturation and developmental systems with TNGS, expect the primary motor cortex to be extensively engaged in controlling stepping and walking. What is unclear from the maturational approach is how to explain the initially highly diffuse activation during early walking (stepping on the treadmill in this experiment) that is inefficient, showing parallels to early reaching. The practice involved to become skillful and efficient with this functional motor skill seems to follow the trajectory observed here for reaching, clearly not attributed to an innate pattern generator.

3.5 Conclusion

To summarize, we have demonstrated the viability of fNIRS technology to document the activity of cortical motor neurons activated during the emergence of neuromotor control as infants perform functional motor skills. Moreover, we have shown that characteristics of cortical activation patterns parallel changes in the skill levels of infants across at least two motor skills and goals. Specifically, when self-initiated motor patterns occur as skills are nascent and have minimal practice, cortical activity is dispersed. Conversely, when infants are highly efficient and the skill is well practiced, as in our reaching task, neural activity reduces and is more specific to the production of the skill. Finally, when skills are unexplored in a goal-directed manner, activity in the primary motor cortex may be undetectable or severely limited. Future research is needed to extend the ages of observation and levels of practice to strengthen and confirm these arguments. In addition, because our data capture were limited to the primary motor cortex, it will be important to expand the regions of interest to include areas deemed critical to establishing control of goal-directed movements, especially the prefrontal cortex and cerebellum. The parallel or prescient activity in these areas may help understand the roles of volition and adaptation in the early development of neuromotor control.

Table 3.1. Average (M) and standard deviation (SD) for anthropometric measurements and the Motor Scale of the Bayley Scale of Infant Development (MS-BSID-III) for each group by task

		Younger				**Older**			
		Reaching		**Stepping**		**Reaching**		**Stepping**	
		M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Age (weeks)		26.22	2.24	27.12	3.86	52.2	1.63	52.1	1.80
Weight (kg)		8.24	0.82	8.24	0.85	9.69	1.28	9.93	1.32
Length (cm)		66.54	2.48	68.12	2.63	76.58	2.66	75.23	2.61
Head Circumference (cm)		43.62	1.40	44.21	1.33	47.12	0.72	47.21	1.08
Inion-Nasion (cm)		26.02	0.93	25.93	0.91	27.34	1.12	27.83	1.83
A1 to A2 (cm)		25.89	0.91	25.87	0.99	27.66	1.71	27.48	1.53
BSID-III (raw score)	**Fine**	20.13	3.00	20.14	3.24	27.75	0.46	27.10	1.29
	Gross	25.13	1.89	25.00	2.00	44.13	4.05	41.50	5.56
	Total	45.25	4.33	45.14	4.63	71.88	4.29	68.60	6.54

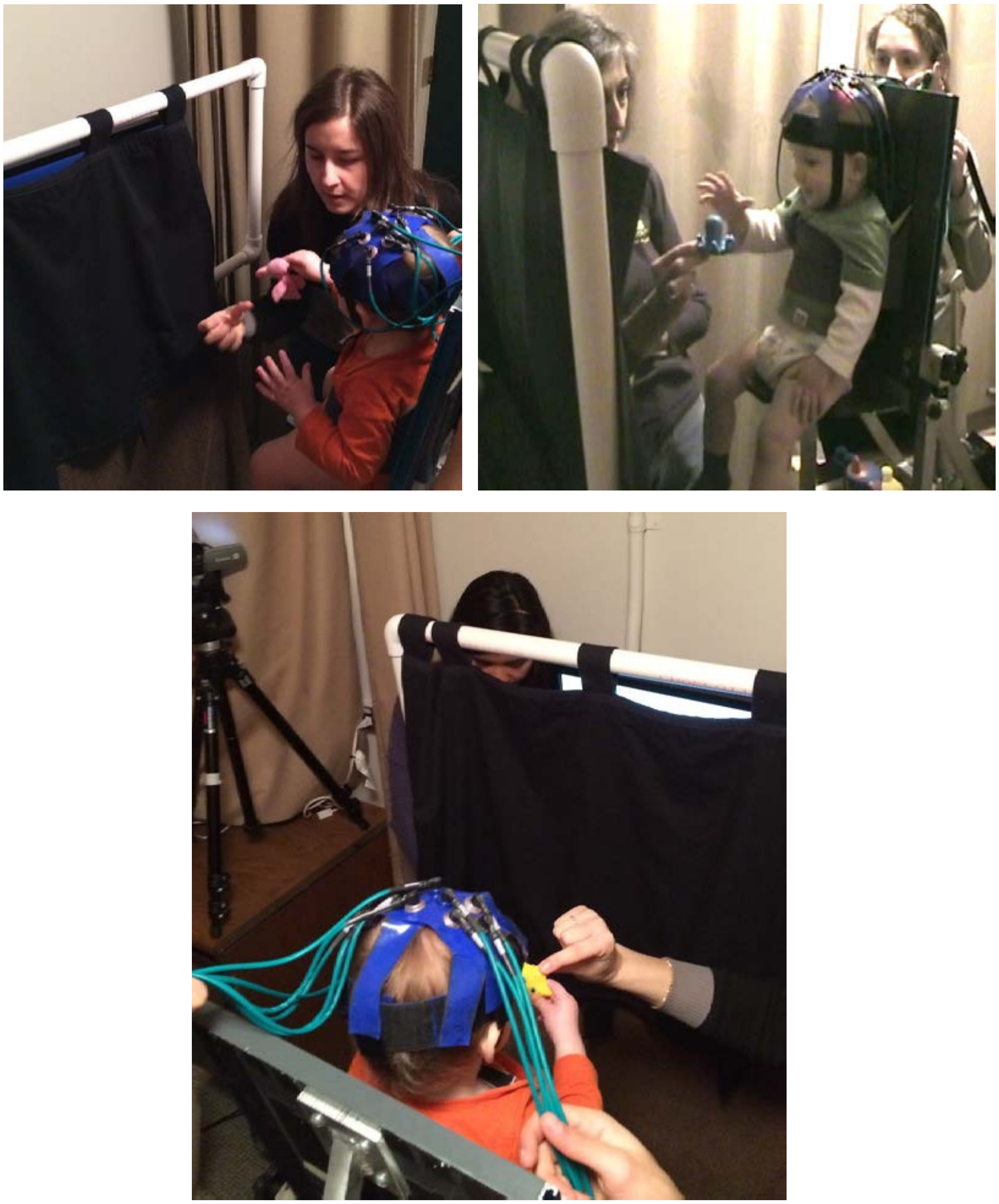


Figure 3.1. Set up for reaching task.

Figure 3.2 Exemplar toys used for reaching.

Figure 3.3. Set up for stepping task.

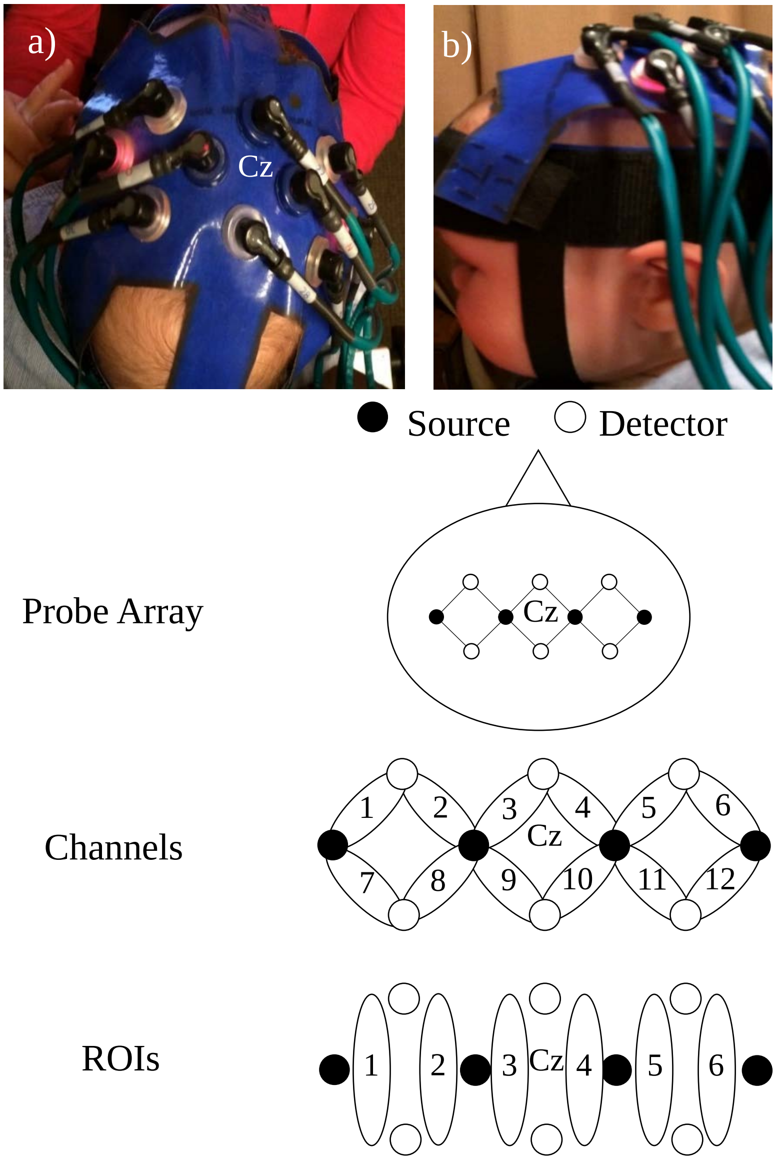


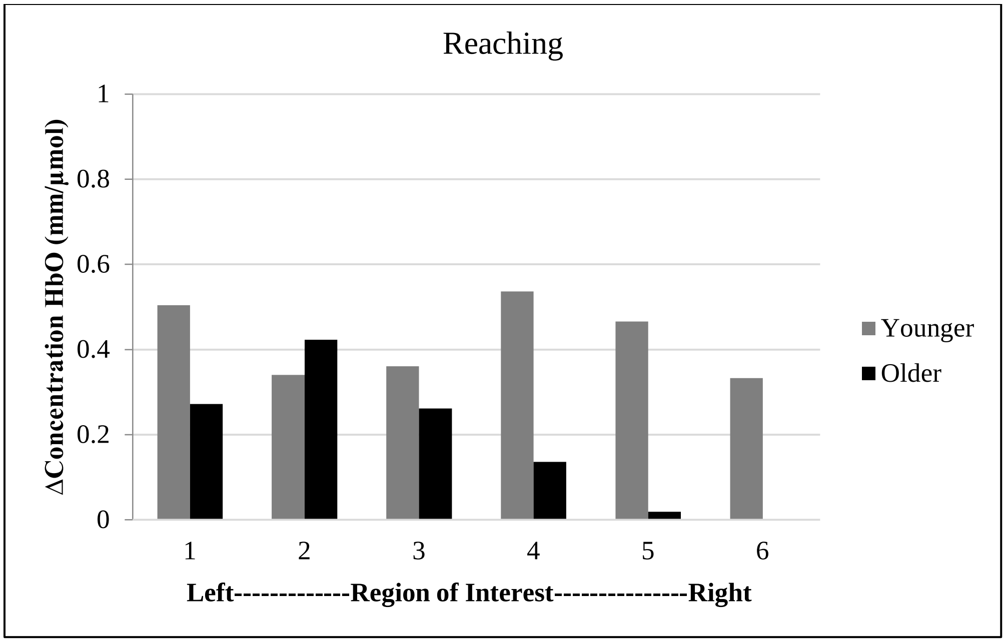
Figure 3.4. Layout of headgear from the a) superior view and b) lateral view of on an infant's head. Diagram and superior view of the c) sources and detectors, d) channels, and e) ROIs.

Table 3.2. Sum of active ROIs (HbO) for each group.

	Reaching		**Stepping**	
Participant ID	Younger	Older	Younger	Older
1	5	1	3	3
2	5	2	2	4
3	5	1	3	4
4	4	4	3	3
5	6	3	3	4
6	6	2	2	3
7	4	4	3	3
8	6	3	2	2
9	4	2	2	4
10	6	5	3	5
11	5	3	3	3
Mean (SEM)	5.09 (0.25)	2.73 (0.38)	2.64 (0.15)	3.46 (0.25)

Table 3.3. Sum of active ROIs (HbR) for each group.

	Reaching		**Stepping**	
Participant ID	Younger	Older	Younger	Older
1	1	0	2	1
2	1	0	0	2
3	3	1	2	4
4	1	1	2	1
5	1	0	2	3
6	1	1	2	1
7	1	1	1	2
8	1	1	2	2
9	1	1	2	4
10	0	1	3	3
11	1	0	1	2
Mean (SEM)	1.09 (0.21)	0.64 (0.15)	1.73 (0.24)	2.28 (0.33)



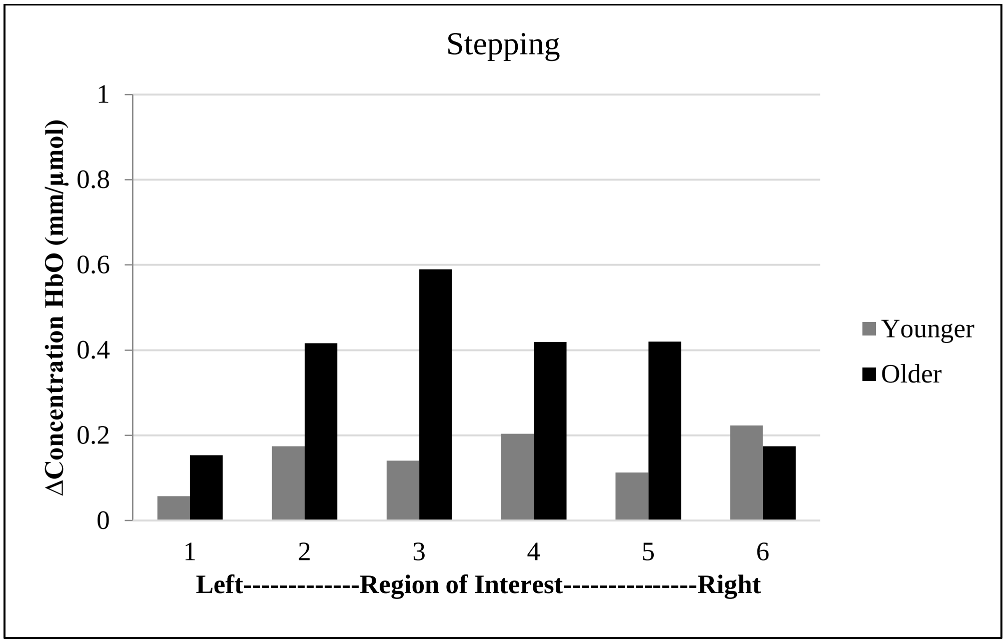
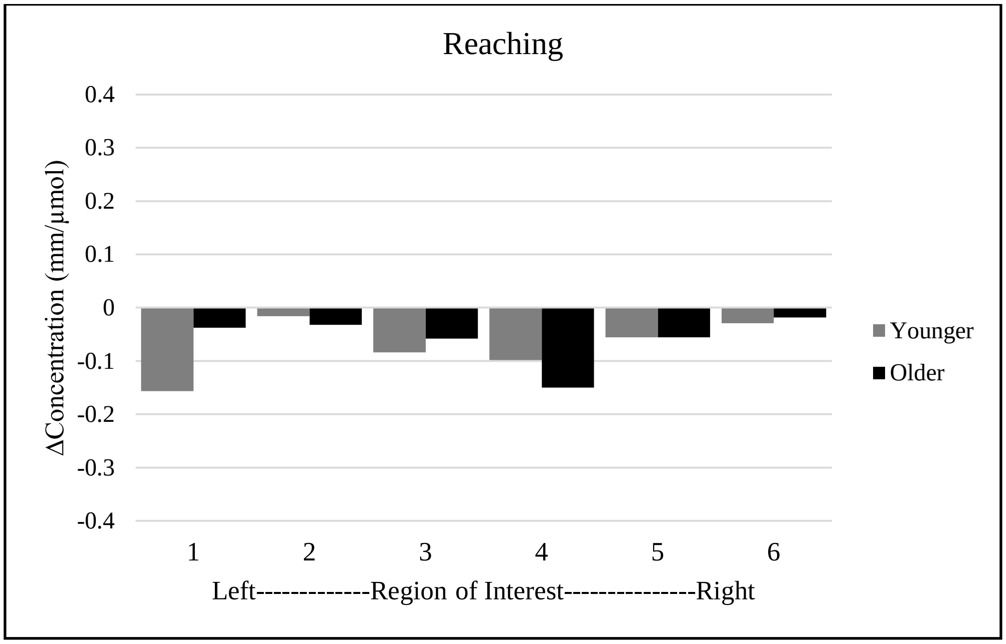


Figure 3.5. Change in concentration of HbO for reaching (top) and stepping (bottom) comparing younger and older infants in the respective ROIs.



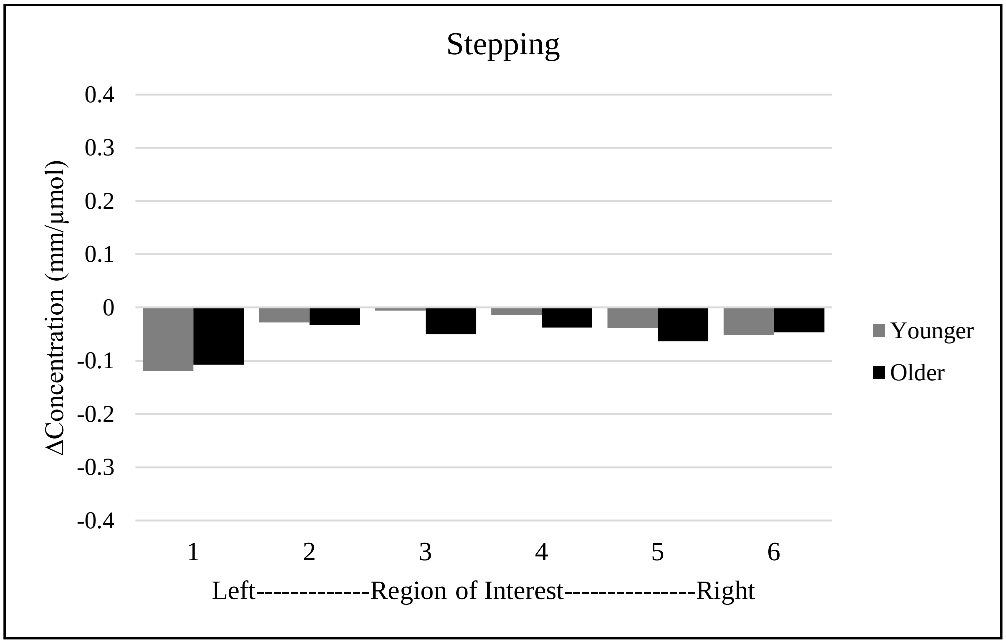


Figure 3.6. Changes in concentration of HbR for reaching (top) and stepping (bottom) comparing younger and older infants in the respective ROIs.

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Chapter IV: Emergence of Cortical Network Activity As Infants Develop Functional Motor Skills

Abstract

In Chapter 3, we examined changes in infant motor cortex activity with age during reaching and treadmill stepping. While the motor cortex is an important brain region for the execution of voluntary movement, skill development draws upon many different subsystems in the brain, each contributing a unique element as skills emerge. Therefore, in Chapter 4, we used fNIRS to quantify hemodynamic activity of the prefrontal cortex and cerebellum, in addition to the motor cortex, as infants performed these same behaviors. Additionally, to explore the emergence of the complex interplay among the three brain regions, we conducted a functional connectivity analysis on time series data acquired from the same set of participants during an unstructured setting in which infants actively reached for, manipulated and explored objects. Twenty-nine infants with typical development [14 younger (*M* = 27.85 ± 1.04 weeks; 9 F) and 15 older (*M* = 49.32 ± 1.41 weeks)] participated in our study. Based on current neuroscience and systems theories, we hypothesized the infants with less or minimal experience with a skill would exhibit more distributed activity within the prefrontal cortex, primary motor cortex, cerebellum compared to infants with more experience with a functional motor skill.

Furthermore, we hypothesized higher connectivity between brain regions in infants with increased experience reaching. Consistent with Chapter 3, younger infants recruited a diffuse area of the motor cortex compared to older infants during reaching. The same pattern for more diffuse activation in younger, less skilled infants was observed in both frontal cortex and cerebellum. For stepping, younger infants recruited a larger area of the prefrontal cortex, a smaller area of the primary motor cortex, and a similar area of the cerebellum compared to older infants. The connectivity analysis did not show increased correlation across channels spanning the three brain regions with increased age. However, within each region, stronger correlations were present in older infants compared to younger infants. Our data suggest that as infants increase experience with a skill, a refined network of activity emerges. That is, an increase in strength in activity within the brain regions as infants improved control of their limbs during goal-directed behaviors. Finally, with increased experience, functionally connectivity within local brain areas emerge while the between brain region connectivity emerges with extensive experience with a skill.

4.1 Introduction

Goal-directed behaviors require both accurate planning and execution to achieve success. Motor researchers' understanding of these processes in adults far exceeds what has been documented in infants. Furthermore, it remains unclear how brain activation patterns change as skill emerges over time in infants; or if the patterns are the same or different as we know it in adults.

The dynamic systems approach has provided a useful framework regarding central nervous system (CNS) development (Byrge, Sporns, & Smith, 2014; Smith & Thelen, 2003; Thelen & Smith, 1994). Theories rooted in the dynamic systems approach posit that new patterns of behavior emerge through self-organization among relevant subsystems, such as the CNS, muscles, and task-specific context. For example, as crawling and cruising emerge, infants must be motivated to traverse space, identify a target or destination, control their head orientation, posture, and produce leg movements to propel themselves forward (Corbetta & Ulrich, 2014; Thelen & Ulrich, 1991). In the months leading up to the onset of independent walking, at about 12 months, infants have been building the necessary strength, control of body segments, and balance to produce alternating leg movements in upright and unsupported posture. As functional motor skills, like cruising and walking, emerge in the first year of life, each of the subsystems, as well, follows its own developmental trajectory. It is through the bidirectional interactions among the CNS, the muscles, repetitions, and context that the system acts as a whole in a coordinated manner. This system response evolves and improves over practice time

(Adolph et al., 2012; Chang, Kubo, & Ulrich, 2009). Thus far, the development of underlying neural activation patterns, one critical subsystem, has been hypothesized through complimentary neuroscience data and theories.

The theory of neuronal group selection (TNGS) is derived from empirical and modeling data and proposes that early brain activity and connectivity changes as and in concert with effects to produce functional behaviors (Edelman, 1987; Sporns & Edelman, 1993). TNGS proposes that early in skill acquisition, there is high redundancy in the nervous system. In infants, this redundancy is manifested in the intrinsic overproduction of unspecified neurons and synaptic connections which facilitates discovery of first many "workable solutions" and then ultimately homing in on ecologically meaningful and efficient goals (Bertenthal & Campos, 1987; Greenough, Black, & Wallace, 1987). Infants activate many different combinations of neurons within local areas (e.g. motor, frontal, cerebellum) as they identify a goal and attempt to achieve it; such as to reach for an object they see or move their bodies through space. After they discover multiple combinations of neural activation that work they select/strengthen connections that are more effective. That is, selection drives much of neural organization. The direct examination of the emergent neural organization and change in human infants during efforts to perform movement patterns has yet to be conducted.

To date, magnetic resonance imaging (MRI) of the infant brain has been used to document the anatomical changes in the brain early in life when infants are at rest or sleeping (Almli, Rivkin, & McKinstry, 2007; Choe et al., 2013; Sanchez, Richards, &

Almli, 2012). These studies have demonstrated the rapid growth in volume in all different brain regions, specifically between the ages of 3 and 13 months post-birth. However, the investigation of the functional changes that underlie the emergence of behaviors has been hampered by the constraints of traditional neuroimaging methodology. Recently, the use of functional near-infrared spectroscopy (fNIRS) has enabled researchers to directly examine the functional neural activation patterns early in life (Emberson, Richards, & Aslin, 2015; Lloyd-Fox, Wu, Richards, Elwell, & Johnson, 2013; Nishiyori, Bisconti, Meehan, & Ulrich, 2016; Southgate, Begus, Lloyd-Fox, di Gangi, & Hamilton, 2014). fNIRS takes advantage of the differential light absorption properties of oxygenated and deoxygenated hemoglobin (HbO and HbR, respectively) to determine regional neural activity (Chance et al., 1998; Obrig & Villringer, 2003; Villringer & Chance, 1997).

To determine the emerging neural basis in motor regions of the brain, we investigated two heavily studied motor behaviors, reaching for a toy and stepping while supported over a treadmill. Reaching emerges over the first 6 months of post-birth life and allows infants to manually explore objects in their immediate environment. For reaching to emerge, infants must be able to visually locate the target, activate the necessary muscles of the arms, control their posture and head, and use proprioception to control their arm trajectory to the target (Thelen et al., 1993). Furthermore, infants fine-tune their actions with the environment and stable patterns of movement form, as they repeatedly attempt to reach for objects (Corbetta & Bojczyk, 2002; Corbetta, Williams, & Snapp-Childs, 2006; Williams, Corbetta, & Guan, 2015).

Later in the first year of post-birth life, infants undergo a similar cycle of experience but with their lower limbs as they attempt to traverse across a larger space through upright locomotion. Voluntary stepping in the form of cruising (walking with support) and independent walking emerges between 9 and 12 months. Furthermore, researchers can elicit, from infants by supporting them on a motorized treadmill, alternating stepping patterns, as well as multiple inter-limb coordination patterns across the first year of life (Thelen & Ulrich, 1991; Thelen, 1986; Ulrich, Jensen, & Thelen, 1991). The treadmill provides a unique and meaningful context in which researchers can consistently test the abilities of infants to respond to a particular context with steps and other behaviors that could not be elicited or observed in a natural setting (Chang et al., 2009; Teulier, Sansom, Muraszko, & Ulrich, 2012; Thelen & Ulrich, 1991). By 9 to 12 months, infants will produce consistent alternating steps on and off the treadmill with support. Thus, the adaptive and changing nature of stepping behaviors, like other behaviors, demonstrate that the subsystems available to produce body segment trajectories including factors external to the infant are softly assembled and can affect the presence or absence of any particular overt behaviors across time.

The present study’s goal was twofold. The first goal was to describe the developmental changes of neural activation patterns of three hypothesized-to-be relevant brain regions as infants acquired functional motor skills. The second goal was to explore activate-state functional connectivity across these same brain regions as infants reached in an unstructured setting. We used fNIRS brain imaging technology to address both goals.

For the first goal, we quantified the hemodynamic response of the prefrontal cortex (pFC), primary motor cortex (M1), and cerebellum (Crbl) during reaching and treadmill stepping for infants at 6 and 12 months of age. These three brain regions were chosen given their known contributions to skill acquisition in adults (Doyon & Benali, 2005; Halsband & Lange, 2006). We chose 6 and 12 months of age, because by 6 months, infants will have had 1 to 2 months of experience with reaching but the behavior is still unstable and will not be fully functional. In addition, at the same age, infants will have had no experience engaging in upright stepping activity, which presents a completely novel task when they are positioned over a motorized treadmill. By 12 months of age, infants will have had at least 6 months of experience reaching, and the behavior has become stable and quite functional. At the same age, infants will have a month or two of cruising practice and just started to take their independent steps.

Early in skill acquisition, TNGS posits that increased numbers of neural circuits are activated. As infants become skilled with their movements, the number of activated neural circuits reduces and the activated circuits and their connections become stronger. Based on this framework, we hypothesized that with increased goal-directed practice performing a skill; infants will shift from a diffuse to focal brain activity in each of the three brain regions. Specifically, during reaching, 6-month old infants will exhibit dispersed area of activity of the M1, pFC, and Crbl, but by 12 months, this activation pattern will become refined as demonstrated by fewer channels detecting significant changes in oxygenation. During treadmill stepping, we hypothesized that 6-month old infants will show a smaller area of activity only in the M1, compared to older infants as we have observed previously (Nishiyori et al., 2016). Moreover, we hypothesized that the pFC and Crbl will exhibit a wider area of activity in 6 month old infants compared to 12 month old infants. The treadmill stepping context is a unique and novel context for both groups of infants. Six-month-olds have minimal experience being supported upright as their legs move out from under them. Thus, infants at this age will be cognitively engaged to resolve the issue of their legs moving away from their body and to understand the goal of the condition. The increased attention to the task will be seen in the larger area of pFC and Crbl activity. Twelve-month-olds will have had 1 to 2 months of experience with upright locomotion; thus they will require less attention to the treadmill stepping task. Infants at this age understand the goal, when their legs move away from their body; thus requiring a smaller area of activity from the pFC. Moreover, because infants at 12-months have developed, although still improving, lower limb control, significant contributions of the Crbl are required in order to control and error-correct lower-limb movements.

For the second goal we quantified the relationship among hemodynamic responses of the prefrontal cortex, primary motor cortex, and cerebellum as infants actively reached and explored toys in an unstructured playtime. Strong correlations between different brain areas are used to infer functional dependency or connectivity during behavior. To date, most studies examining functional connectivity have occurred during simple tasks in adults such as wrist flexion and extension (Heitger et al., 2013) and visuomotor tasks (Langan et al., 2010). The limited work in infants has occurred while they were sleeping (Damaraju et al., 2014; Fransson, Åden, Blennow, & Lagercrantz, 2011; Smyser, Snyder, & Neil, 2011). Based upon this work and the principles of the dynamic systems approach and TNGS, we hypothesized older infants with experience with goal-directed reaching would demonstrate stronger connectivity within and across the pFC, M1, and Crbl compared to younger infants.

4.2 Method

4.2.1 Participants

We consented 40 infants, 20 6-month-olds and 20 12-month-olds. Of these, two of the younger infants and three of the older infants became fussy during the preparation for testing which did not allow us to collect data. In addition, two of the younger infants and two of the older infants' data were unusable due to extensive noise, motion artifacts, or too few usable channels. This resulted in 16 younger and 15 older infants for who we had usable data for reaching and/or stepping. Not all infants' data were usable from both tasks, thus the final numbers, ages and gender for each task and age group were: reaching = 14 younger (*M* = 27.85 weeks, range = 25.22 -28.21 weeks, 9 females) and 15 older (*M* = 48.24 weeks, range = 48.75-54.11 weeks, 8 females); stepping = 14 younger (*M* = 26.31 weeks, range = 25.02-27.32 weeks, 9 females) and 15 older (*M*= 48.24 weeks, range = 47.67-52.72 weeks, 7 females); unstructured play = 14 younger (*M* = 27.85 weeks, range = 25.22 -28.21 weeks, 9 females) and 15 older (*M* = 48.24 weeks, range =

48.75-54.11 weeks, 8 females). Table 4.1 contains the summary of participant characteristics.

4.2.2 Session Overview

The present study followed a similar protocol to a previous study (Nishiyori et al., 2016). Briefly, upon arrival at the fNIRS lab, we allowed infants to acclimate to our space by playing with toys and interact with the research team. During this time, a research team member explained the study to parents and answered any questions parents had. Parents read and signed the informed consent. Next, we removed infants’ clothing except their shirt and diaper to allow infants to move freely. We measured the infant's head circumference, distance between inion and nasion, and between left and the right pre-auricular points to identify FPz according to the 10‑20 international system (Jasper, 1958). After we placed the infant into the customized infant seat, we secured the headgear on the infant's head. Floor to ceiling curtains were approximately 60 cm away from both sides of the table on which the infant seat rested, which minimized the amount of distraction due to open space. We began testing with the reaching task, followed by a brief break and then tested the treadmill stepping task. During the break, we re-arranged the lab to prepare for the stepping task. After completing the treadmill stepping task, we re-arranged the lab to prepare for the unstructured play condition. After the unstructured play condition was complete, we took photographs of the headgear on the infants to confirm the optodes/headgear had not moved from the target areas, as this could affect the quality and precision of our fNIRS measurements. We then removed the headgear and took basic anthropometric measurements (e.g., weight, total body length, leg (thigh and shank) length and circumference, and thigh and umbilicus skinfold). Finally, we administered the Motor Subscale of the Bayley Scales of Infant Development III (BSID-III, Bayley, 2006).

4.2.3 Tasks

4.2.3.1 Reaching

For the reaching task, infants were secured with a wide soft chest strap in a customized infant seat (seat pan was 32 cm above the table top, backrest: 75 cm long, and reclined approximately 10° from the vertical). The infant seat was secured to the top of a table [117.4 (L), 59.5 (W), 79.5 cm (H)], so that infant's head would be at eye level with the video monitor. We positioned a video monitor (23” LCD, Phillips, Andover, MA, USA) on a cart in front of and approximately 80 cm away from the seat. We hung a thick black curtain in front of the monitor that could be opened and closed to hide the monitor during reaching trials and revealed videos playing during the rest phase. For reaching trials, a variety of age-appropriate small grip-sized toys [5 (L) × 5 (W) × 5 cm (H)] were presented to elicit reaching and maintain interest.

For the task phase, an experimenter presented the toy at the infant's midline within reach, followed by a rest phase. The experimenter first retrieved the toy from the infant, then unveiled the monitor playing an infant entertainment video (e.g., Baby

Einstein) intended to keep the infant calm and still for a minimum of 20 s (rest phase). If after 10 s from toy presentation, the infant did not reach for the toy we presented, we began a rest phase then started a new trial with a new toy. We repeated the cycle of reaching and rest for a minimum of 10 successful trials.

4.2.3.2 Stepping

We placed our custom-designed treadmill [frame: 93.5 (L) × 43.7 (W) × 21 cm (H); belt: 81.5 (L) × 30.6 cm (W)] on top of and near the front edge of the same table used for reaching, in the center of the room. Each trial consisted of a rest-phase followed by a stepping phase. We started with a 30 s rest phase. During the rest phase, the experimenter held the infant who rested against the experimenter's chest. From pilot sessions, we determined that this was the best position to keep the infant calm and minimize movements thus optimizing rest phase status and values. Following the rest phase, each treadmill trial lasted 30 s. During each trial, an experimenter supported the infant under the arms so they were upright with feet touching the belt surface. Infants were encouraged to support as much of their weight as they could; experimenter provided supplemental weight support and posture control. The treadmill belt speed was set at .20 m/s for both younger and older infants based on previous research which showed this to be the most effective speed to elicit alternating steps in infants across the first year of life (Teulier et al., 2009). If infants did not respond to the moving belt with any leg movements during a trial, that is, they allowed their legs to drag and extend behind them, we lifted the infant up to bring their legs forward and placed them on the belt again to encourage the desired motor response - stepping. We collected a minimum of 10 stepping trials, in which infants responded to the moving treadmill belt with leg movements.

4.2.3.3 Unstructured Play

We positioned infants in a seated position inside a nursing pillow that was positioned at the center of a large blanket. This blanket was positioned in the center of the room. An experimenter sat directly across from the infant and a research assistant sat behind the infant to provide any postural adjustments or reposition the infants if they moved outside of the nursing pillow.

Once the infants were positioned in the nursing pillow, the experimenter started by presenting small grip-sized toys that were used during the reaching task. The experimenter presented toys continuously to maximize the number of reaching trials. If infants become fussy, we presented them with other types of toys, such as those that were visually engaging and/or make noises. We aimed to measure a minimum of six minutes, in which infants were actively reaching for or manually exploring the toys. We chose 6 minutes, because this is the suggested window of time in order to conduct a connectivity analyses during this active state (Smyser et al., 2011). Thus, their behaviors included maintain seated posture, looking at toys, reaching for toys, manually and orally exploring toys, and other spontaneous arm movements.

4.2.4 fNIRS Data Acquisition

The fNIRS data were acquired with the same fNIRS system and in a similar procedure described in Nishiyori et al. (2016). The only difference was in the number and configuration of the optodes. In the present study, the headgear contained a total of nine source- and sixteen detector-optodes placed approximately 2.5 cm apart creating a 28-channel array (Figure 4.1). There were three separate arrays for each of the three regions (Figure 4.2). Fourteen channels covered the bilateral frontal area, from F7 to F8. Eight channels covered the bilateral M1 area, from C3 and C4, centered on Cz. Finally, six channels covered the bilateral cerebellar area, in which the most superior channels were positioned between Oz landmark and the Inion (Schutter & van Honk, 2006).

4.2.5 Video Recording

We used a digital camcorder (Canon, Melville, NY, USA) that sampled at 60 Hz to record reaching and treadmill stepping tasks, and the unstructured play condition. During the reaching task, the camera was mounted on a tripod positioned at a 45° from midline and 100 cm away from the center of the infant seat. During stepping trials, the camcorder was repositioned perpendicular to the side of the treadmill. For the naturalistic condition, the camera was positioned approximately 45° from the midline and 120 cm away from the infant. These camera positions allowed us to view any gross movements of the headgear and fNIRS cables. The onset of task and rest phases, and any undesired behaviors, such as crying and head turning, were documented. The camcorder and fNIRS system were synchronized via an audio signal. At the start of each condition, we inserted an audio signal simultaneously to the video and fNIRS data. We then mapped the timing of the onset of reaches and treadmill steps and the start of the rest phases onto the fNIRS data to identify functional movement-related changes in hemodynamic activity of the three regions.

4.2.5 Bayley Scale of Infant Development – Motor subscales

At the end of the session, we administered the Motor Subscale of the Bayley Scales of Infant Development (BSID-III, Bayley, 2006). This scale allowed us to characterize the status of gross and fine motor skill acquisition between and within the two groups.

4.2.6 Trial Rejection

To determine the usability of trials, all videos were behavior-coded offline by two different researchers. For reaching, trials were valid if the infant reached for and successfully grasped the object. Trials were not considered for further analysis if infants did not reach for the object. For the treadmill stepping context, trials were valid if the infant stepped in response to the moving belt. Trials were not considered for further analysis if infants did not step in response to the moving belt for more than half of the 30-sccond trial. For example, if the infant allowed her legs to drag behind them for a majority of the trial, we did not code this as a successful trial.

4.2.7 fNIRS Data Processing

fNIRS data were processed using the Homer2 (Huppert, Diamond, Franceschini, & Boas, 2009) Matlab toolbox (Mathworks, MA). Data were low-pass filtered at .8 Hz and then motion-corrected using a wavelet-based filtering (Molavi & Dumont, 2012).The optical density signal was then converted into concentration using the modified Beer–Lambert Law. Partial path-length factor was set at 6.0 and the known coefficients of oxygenated (HbO) and deoxygenated (HbR) hemoglobin (Cope et al., 1988; Obrig & Villringer, 2003). Concentration data were then time locked to movement onset and epoched. For the reaching task the epoch consisted of 3 s prior to and 10 s post onset of reach. For the stepping task, the epoch was 1 s prior to and 10 s post onset of stepping. Epochs were averaged for each channel, group, and task and baseline corrected to pre-movement period. Outlier trials in which task-related change in HbO and HbR exceeded two standard deviations were excluded from further analysis. With this criterion, 18.2% of the total 580 test trials from reaching and stepping (29 participants x 2 tasks × 10 trials) were excluded.

For the unstructured play condition, data were pre-processed with the same parameters as the data from the reaching and treadmill stepping tasks. For this condition, hemodynamic activity was recorded continuously until we accumulated a minimum of 6 minutes in which the infants were actively reaching, manipulating and/or exploring the toy. In some cases, we successfully collected a continuous 6-minute bout of reaching. If infants became fussy, however, the research team interacted with them to calm them down before proceeding with more reaches. As a result, there were cases in which we collected shorter bouts (minimum of 2 minutes) of reaching with intermittent calming phases, which were later concatenated to reach 6 minutes. Each infant included in the analyses successfully completed a minimum of 6 minutes of active reaching.

4.2.8 Data Analysis

For the reaching and stepping tasks, three dependent variables of interest were extracted from the data. First, in order to determine the number of functionally active channels, the change in HbO values from each channel within the epoch were used. We used an independent samples t-test to detect any significant changes between pre- and post-onset of the movement for all trials. This test provided the number of channels demonstrating task-related activity, which were then compared across group for each task using separate independent t-tests. The dependent variable of number of active channels was quantified as a tally of significant channels for each infant in each task. The same analysis was performed for HbR. Second, percent signal change was calculated based on the change of concentrations for both HbO and HbR compared to rest values within an epoch. We then determined group differences in peak activity by comparing percent signal change in the channel that exhibited peak HbO change from each participant. Separate independent samples t-tests were performed for reaching and stepping. Finally, we summed the percent signal change of the active channels to calculate the volume of activity during a task. The volume of each HbO (sum of percent signal change across active channels) across groups was compared for each task using separate independent samples t-tests for each task. Volume derived in this manner provides an indication of percent signal change across significant channels. In conjunction with the number of active channels and peak signal change, it can provide information about the focality of cortical activity that neither the number nor peak signal change alone can provide.

Functional connectivity within and across the 28 channels distributed across the three brain regions of interested was assessed using correlation coefficients (*r*) between each possible pair of channels. For each infant, we calculated the correlation coefficients with the 6 minutes of filtered and motion-corrected signal from the unstructured condition. There were 378 *r* values produced for each infant representing all pairs of channels [(28 x 27)/2]. We calculated the average *r*-value for each pair of channels for each group. Then, we compared these *r*-values between groups by using the Fisher r-to-z transformation. This comparison identified which pairs of channels' correlated activity changed between younger and older infants.

4.3 Results

The Bayley data revealed that younger infants, as expected, achieved fewer items, 46 (SD = 4.51), than older infants, 73 items (SD = 4.14). The scores were tightly clustered for each age group; therefore we could not make meaningful comparisons with the fNIRS data. Table 4.1 contains the breakdown of fine motor, gross motor, and total scores from the participants.

4.3.1 Reaching

In the younger group, an average of 10.4 (SD = 2.1) right-handed, 10.8 (SD = 2.7) left-handed, and 9.2 (SD = 3.3) two-handed reaching trials were valid and included in the data analysis. In the older group, an average of 11.1 (SD = 2.3) right-handed, 9.3 (SD = 2.2), and 11.4 (SD=2.0) two-handed reaching trials were considered valid and included in the data analysis. The analyses for differences in the peak percent signal change in HbO revealed no differences between younger and older infants across all channels.

In the M1, the independent *t*-test revealed that during right-handed reaches, younger infants (6.29 ± .83) showed activity in more channels than older infants [3.57 ± 1.74, $t(27) = 4.67$, $P < .001$]. Similarly, the volume of activity was significantly lower in younger infants (.22 ± .055 μM) compared to older infants [1.02 ± .55 μM, $t(27) = 8.4$, $P < .001$]. During left handed reaches, younger infants (5.79 ± 2.67), showed activity in more channels than older infants [3.42 ± 1.55, $t(27) = 5.62$, $P < .001$]. Volume of activity was significantly lower in younger infants (.48 ± .12 μM) compared to older infants [1.44 ± .63 μM, $t(27) = 11.17$, $P < .001$]. During two-handed reaches, younger infants (5.36 ± 1.15) showed activity in a similar number of channels as older infants [4.50 ± .854, $t(27) = 3.53$, P = .002]. Volume of activity was significantly lower in younger infants (.08 ± .16 μM) compared to older infants [.27 ± .11 *μM*, $t(27) = 12.89$, $P < .001$].

In the pFC, the independent *t*-test revealed that during right-handed reaches, younger infants (9.79 ± 1.53) showed activity in more channels than older infants [5.57 ±

1.45, *t*(27) = 2.77, *P* = .01]. Volume of activity was significantly lower in younger infants (.73 ± .18 μM) compared to older infants [1.54 ± .85 *μM, t*(27) =9.7, *P* < .001].During left-handed reaches, younger infants (8.64 ± 1.95) showed activity in more channels than older infants [5.21± 1.19, *t*(27) = 5.58, *P* < .001]. Volume of activity was significantly lower in younger infants (.25 ± .06 μM*)* compared to older infants [1.7 ± .62 μM, *t*(27) =8.7, *P* < .001]. During two-handed reaches, younger infants (8.57 ± 1.91) showed activity in more channels than older infants [6.07 ± 1.73, *t*(27) = 3.07, *P* = .005]. Volume of activity was significantly lower in younger infants (.08 ± .02 μM) compared to older infants [.27 ± .1 μM, *t*(27) = 7.5, *P* < .001].

In the cerebellum, the independent t-test revealed that during right-handed reaches, younger infants (4.36 ± .929) showed activity in more channels than older infants [2.21 ± .699, *t*(27) = 2.56, *P* = .017]. Volume of activity was significantly lower in younger infants (.53 ± .69 μM) compared to older infants [2.4 ± .59 μM, *t*(27) = 12.2, *P* < .001]. During left-handed reaches, younger infants (4.42 ± 1.09) showed activity in more channels than older infants [2.71 ± 1.27, *t*(27) =5.34, *P* < .001]. Volume of activity was significantly lower in younger infants (.70 ± .17 μM) compared to older infants [1.82 ± .61 μM, *t*(27) = 6.61, *P* < .001]. During two-handed reaches, younger infants (4.29 ± 1.44) showed activity in more channels than older infants [3.21 ± 1.19, *t*(27) = 5.82, *P* < .001]. Volume of activity was significantly lower in younger infants (.11 ± .05 μM) compared to older infants [.4 ± .1 μM, *t*(27) = 9.71, *P* < .001].

4.3.2 Treadmill Stepping

An average of 8.3 (SD=3.2) and 9.6 (SD=2.2) stepping trials were valid and included in the data analysis for the younger and older group, respectively. Similar to the reaching data, the comparison of peak activity in the channels did not detect any significant differences.

In the M1, younger infants (3.07 ± 1.20) showed activity in fewer channels than older infants [6.0 ± 1.04, *t*(27) = 2.96, *P* = .006]. Volume of activity was not significantly different between younger (1.35 ± .36 μM) and older infants [1.55 ± .39 μM, *t*(27) = 1.4, *P* = .17].

In the pFC, younger infants (8.42 ± 1.70) showed activity in more channels than older infants [7 ± 1.71, *t*(27) = 2.53, *P* = .017]. Volume of activity was significantly lower in younger infants (1.3 ± .83 μM) compared to older infants [2.6 ± .33 μM, *t*(27) = 5.34, *P* < .001].

In the Crbl younger infants (4.14 ± .864) showed activity in similar number of channels compared to older infants [3.96 ± .770, *t*(27) = .925, *P* = .363]. Volume activity was not significantly different between younger (.84 ± .23 μM) and older infants [.83 ± .21 μM, *t*(27) = , *P* = .90].

4.3.3 Unstructured play

During the unstructured condition, younger infants, on average, reached for toys 23 times [right-handed = 9; left-handed = 8; two-handed = 6], while older infants reached

32 [right-handed = 12; left-handed = 7; two-handed = 12] times within the 6-minute window.

The average correlations across all 378 channel-pairs for younger and older infants are shown in Figures 4.3 and 4.4, respectively. Figures 4.5 and 4.6 highlight those correlations that were statistically significant. In younger infants, all 9 channel-pairs were located within the same local brain region (Figure 4.5). For older infants, 49 channel-pairs were significantly correlated (Figure 4.6). In addition to a increased number of significant channel-pairs within a region, older infants also showed a cluster of significant correlations between channels located in the pFC and Crbl (Figure 4.6). Moreover, the critical *r*-value for a sample of 15 (df = 13) in the older group was 0.51. Based on this value, there were 49 pairs of channels that were significantly correlated (Figure 4.6).

Although there were qualitative differences in the number and distribution of significant correlations, the Fisher r-to-z transformation showed only 3 pairs of channels were significantly different between the younger and older groups. These included pair of channels within each brain region [channels 7 and 8 (M1), channels 18 and 20 (pFC), and channels 25 & 26 (Crbl), Figure 4.7]. In all three pairs of channels, the connectivity was higher in older infants compared to younger infants.

4.5 Discussion

The present study aimed to describe the emerging neural network that underlies the development of functional motor skills in the first year of life. Guided by the framework of the dynamic systems approach (Byrge, Sporns, & Smith, 2014; Smith & Thelen, 2003; Thelen & Smith, 1994) and TNGS (Edelman, 1987; Sporns & Edelman, 1993), we hypothesized refined neural activation patterns would emerge in the developmentally advanced older infants due to practice. Thus, we predicted a larger area of neural activity within each brain region when the tested skills were emerging or novel, and unstable. Moreover, we predicted that activity would be refined or localized as skills become stable and functional when infants have had increased experience using the motor skill. The results of our current study supported our predictions. Across the three brain regions, our results demonstrated the predicted changes in functional activation across ages and tasks. Our functional connectivity data showed increased correlations during reaching in neighboring channels, within local regions, in older infants compared to younger infants. The developmental change in network activity among the three regions demonstrates the functional cortical development is associated with the increase in experience with specific motor outcomes.

4.5.1 Neural Activity during Reaching

Our findings regarding developmental changes in M1 reinforce our previously published results (Nishiyori et al., 2016). The current work extended those data by showing that prefrontal cortex and cerebellar activity follow a similar pattern of change between younger and older infants. That is, as infants shift from being nascent reachers to skilled reachers with practice, neural activation patterns are refined.

Reaching is functional but not stable by 6 months of age. Younger infants are able to drive the target muscles to reach but also activate other muscles (coactivation) that they have not learned to inhibit or control (Nishiyori, et al., 2016). When reaching for a toy, infants are visually engaged with the objects and must be excited by or attracted to the toy in order for them to attempt to acquire the object. Younger infants are easily distracted by the visually stimulating field and require increased resources of areas commonly known to contribute to the role of attention, in order to focus on the toy that they reach for. Our data shows that younger infants activated the prefrontal areas, specifically around the dorsolateral prefrontal cortex (DLPFC), which is defined in neuroscience as the decision-making and attention-to-task area (Grossmann, 2013). Our data show that younger infants utilize a larger area of the DLPFC over successive reaches during the early stages of motor learning and control. Furthermore, the activity of the pFC area in the context of reaching can also be explained by increased errors during the early phases of skill acquisition, which have been shown in adult motor learning tasks (Halsband & Lange, 2006). At 6 months of age, infants are still exploring and learning strategies to control their body in the best way while reaching for a toy.

At 6 months, infants are learning ways to control their posture and balance in a seated position. Moreover, when infants move their arms away from their bodies, in an attempt to reach for a toy, their intrinsic dynamics change and must regain balance. Infants around this age have been shown to coactivate the muscles of their arms and shoulders, and are exploring the most efficient method to successfully reach for the toy, when they have just started to become successful at reaching. The active control of posture and balance engages the Crbl. Six-month old infants are still developing anticipatory postural control, which relies on the feed forward processing of information (Baumann et al., 2015). Furthermore, the cerebellum is controlling, online, the loss of balance when infants are reaching for toys but are still developing the necessary and adequate postural control.

By 12 months, infants are skilled reachers and have refined their neuromotor patterns instead of increasing their task-specific motor cortical representations (Nishiyori, et al., 2016). Our 12-month-olds have had significantly more experience, and successful attempts of reaching (i.e. less errors). Compared to 6-month-olds' reaching data, our 12-month-olds showed reduced area of activity surrounding the DLPFC in, which suggests that infants at this age are efficient in their selection of action, thus requiring less attentional resources when reaching for a toy. Moreover, our older infants have had extensive experience reaching for objects, thus their postural control has improved and hand trajectories towards the target are more efficient (Bertenthal & Von Hofsten, 1998; Harbourne, Lobo, Karst, & Galloway, 2013; Thelen & Spencer, 1998). The refinement of Crbl activity by 12 months, reflects the improvements in balance, postural and hand control when reaching for a toy. Furthermore, the Crbl provides feedback to areas such as the DLPFC and M1 during motor learning tasks, and processes feedback information and integrates sensory input, such as visuomotor information, to guide motor output signals

(Baumann et al., 2015). The refinement of Crbl activity in our older infants could be explained by the reduced contributions of feedback to the DLPFC and M1, as the movement accuracy has improved by this age.

4.5.2 Neural Activity during Stepping

The developmental changes in M1 activity during stepping also follow the same pattern reported in our earlier study (Nishiyori et al., 2016). That is, younger infants activated a smaller area compared to older infants. Similar to reaching, we found a disperse-to-focal pattern of change in the activity of the prefrontal cortex. Unlike reaching, however, we did not see a change in the area of activity in the cerebellum between younger and older infants.

Stepping upright is a behavior that 6-month-old infants exhibit only when researchers provide the moving treadmill belt and bodyweight and postural support. Specifically, younger infants in our study had no experience moving their lower limbs in alternation in the upright posture. As a result, stepping at this phase in development, may not elicit significant M1 activity in this context, in which there is an absence of a volitional intent to produce any particular action pattern (Nishiyori et al., 2016). Interestingly, the activation of the prefrontal cortex at some level shows that infants, even at 6 months are actively engaged with the context. Given the secure handling provided to their trunk, infants may simply try to keep their feet from moving out from under their bodies. The novel context requires infants to be cognitively engaged, as they explore strategies to keep their legs under their bodies.

By 12 months, infants have traversed space voluntarily by scooting, crawling, cruising, and perhaps walking. They are experienced using the DLPFC to attend to relevant information and make decisions above responding, thus, they have begun to refine these population of local neural links, which they can access during the treadmill stepping condition. Thus, older infants, according to our data, activated a smaller area of the DLPFC compared to younger infants. Moreover, older infants may exhibit more consistent alternating stepping patterns but the control of these patterns does not stabilize until later in childhood. As a result, infants are still developing early functional control of their lower limbs, which could explain the lack of difference in our cerebellar data between the younger and older infants. The lack of refinement in our Crbl data during the treadmill stepping condition, could also be explained by the different role that the Crbl plays at different phases in skill acquisition. That is, in 6-month-olds, the Crbl could be contributing to the cognitive strategies that are being explored in the novel context, whereas in 12-month-olds, the Crbl is providing feedback and online control of movements, similar to our 6-month-old reaching data.

4.5.3 Network Activity

The comparison of correlations across all channels between younger and older infants revealed significantly higher connectivity in 3 pairs of channels. The r-values from these 3 pairs were significantly higher in the older infants compared to younger infants. Moreover, we did not detect differences in the inter-regional pairs of channels during the unstructured-play condition. The increased connectivity within brain regions seen in our older infants, compared to younger infants, demonstrates the strengthening of local areas when infants are actively reaching for, manipulating, and exploring toys.

Previous reports have shown that experience-dependent changes in cortical organization take place (Bell & Fox, 1996; Corbetta, Friedman, & Bell, 2014). Each of these studies showed an inverted U-shape pattern in the development of coherence related to an infant's crawling (Bell & Fox, 1996) and walking (Corbetta, Friedman, & Bell, 2014). These studies showed when infants were at novices of a skill, coherence between lateral and frontal electrode sites (F7 and C3) were higher compared to those with more experience with the same skill. Similarly, in our data, we showed that younger infants during the unstructured play condition exhibit significant correlations within local areas within a brain region. Older infants, who have much more experience reaching and exploring toys, as they showed during this condition, showed significant correlations in more local areas within a brain region, as well as between brain regions. Perhaps, infants become more experienced, beyond 12-months of age and into the 2nd year of post-birth life, functional connectivity within local brain areas will decrease as more global and between-brain region connectivity will become strengthened.

Data from the naturalistic condition parallel our findings from the reaching condition. In our reaching data, younger infants showed a lower volume of activity in all three regions during all types of reaches compared to older infants. This suggests that as infants are improving the control of their upper limbs and posture, there is an increase in the strength of activity within each of those regions. The connectivity data revealed a similar pattern. That is, two neighboring sites within the same broad brain region are increasing their connectivity. Our two sets of data further support the experience-dependent change in neural firing patterns.

4.6 Conclusion

In conclusion, we have demonstrated the utility of using fNIRS to document the developmental changes across three motor-brain regions as infants perform functional motor skills. This study has shown the changes in both prefrontal cortex and the cerebellum as functional motor skills emerge. To the best of our knowledge, this is one of the first studies to quantify cerebellar activity in infants using fNIRS.

Similar to previous work (Nishiyori et al., 2016), our study shows that when functional motor skills are nascent and novel, the underlying neural activity is dispersed. As infants make self-initiated and goal-directed attempts, their motor outcomes become more efficient and successful. Similarly, the neural activity becomes refined. This refinement is further described by the increase in connectivity within brain regions as infants improved the control of their upper limbs. Thus, as skills improve the strength in activity increases, which supports the experience-dependent changes in neural activity early in life. This suggests that, as brain activation patterns emerge similar to the patterns identified in early muscle activity and movement patterns. Further research is warranted to describe the specific experience-dependent changes in neural activity in the three regions we investigated. For example, future research could explore the dose-based changes in physical activity or object manipulation to test if experience-dependent changes in brain activity could be enhanced or altered. Furthermore, our data were limited to two age-specific groups, thus future work should incorporate different age groups based on specific amounts of experience with a skill. Finally, our data shed light on the volition and adaptation in early development of neuromotor control, which may help understand how infants with disabilities acquire new functional motor skills.

Table 4.1. Average (M) and standard deviation (SD) for anthropometric measurements and the Motor Scale of the Bayley Scale of Infant Development (MS-BSID-III) for each group by task.

		Younger						**Older**					
		Reaching		**Stepping**		**Unstructured Play**		**Reaching**		**Stepping**		**Unstructured Play**	
		M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Age (weeks)		27.85	2.41	26.31	2.36	27.85	2.41	49.32	2.08	48.24	2.26	49.32	2.08
Weight (kg)		8.61	0.72	8.54	0.81	8.61	0.72	9.72	1.31	9.94	1.06	9.72	1.31
Length (cm)		67.24	2.57	68.13	2.49	67.24	2.57	76.41	2.84	77.82	2.18	76.41	2.84
Head Circumference (cm)		43.31	1.40	43.68	1.33	43.31	1.40	48.03	0.94	47.82	1.35	48.03	0.94
Inion-Nasion (cm)		26.13	0.74	25.95	1.12	26.13	0.74	27.72	1.30	28.06	1.71	27.72	1.30
A1 to A2 (cm)		25.82	1.02	26.03	0.90	25.82	1.02	27.81	1.66	27.44	0.96	27.81	1.66
BSID-III (raw score)	**Fine**	20.9	2.86	20.6	2.74	20.9	2.86	27.80	0.51	27.12	27.80	0.51	0.51
	Gross	25.21	1.71	25.61	1.94	25.21	1.71	43.82	4.06	42.44	43.82	4.06	4.06
	Total	46.11	4.51	46.20	3.68	46.11	4.51	72.86	4.14	69.56	72.86	4.14	4.14

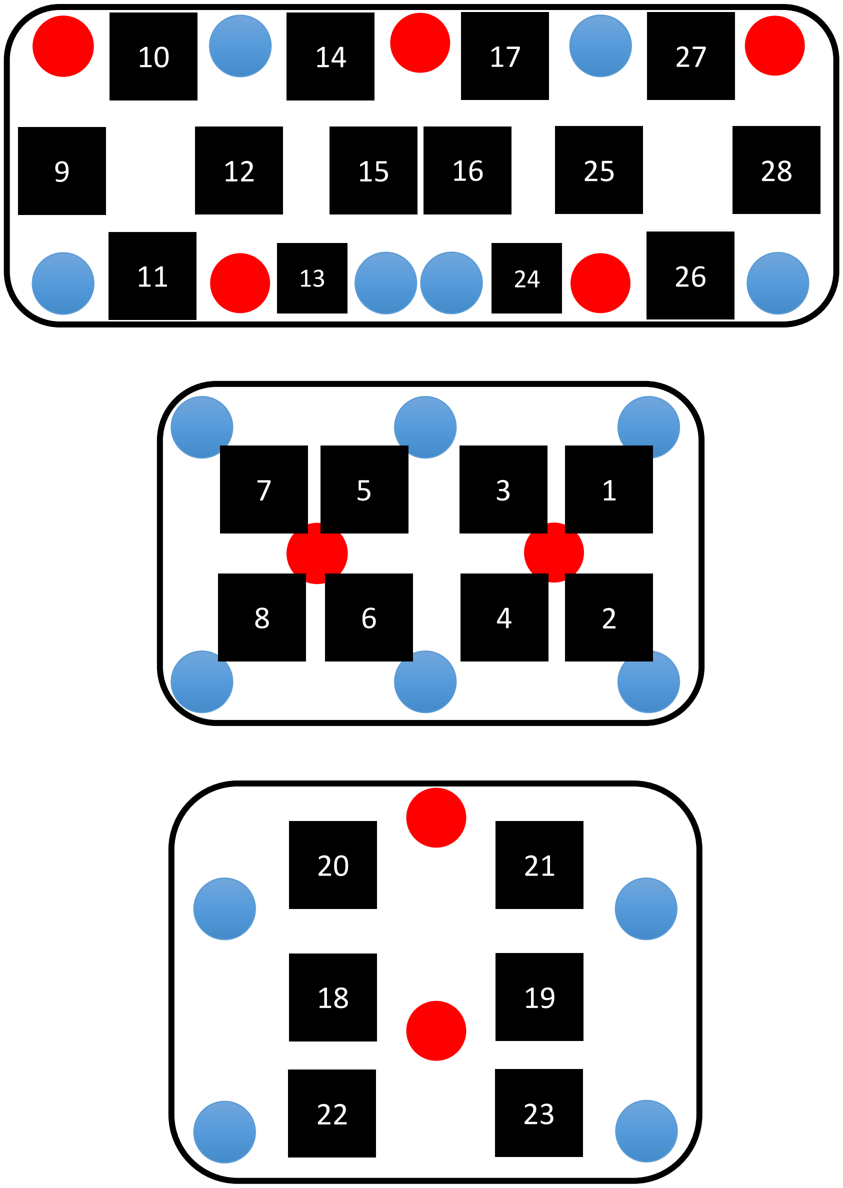


Figure 4.1. Channel numbers (black squares) for each brain region. Red circles represent sources and blue circles represent detectors.

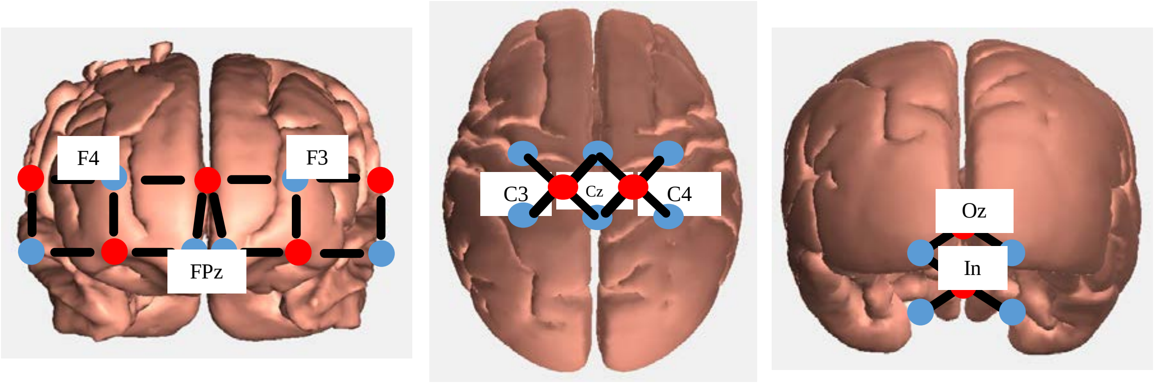
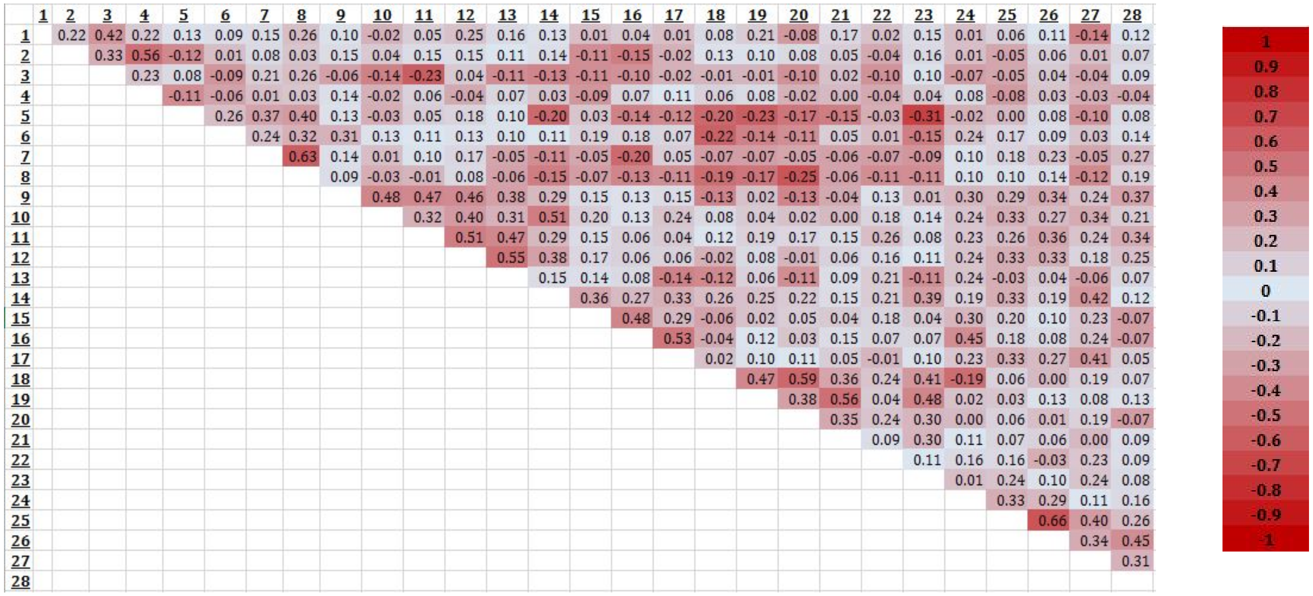
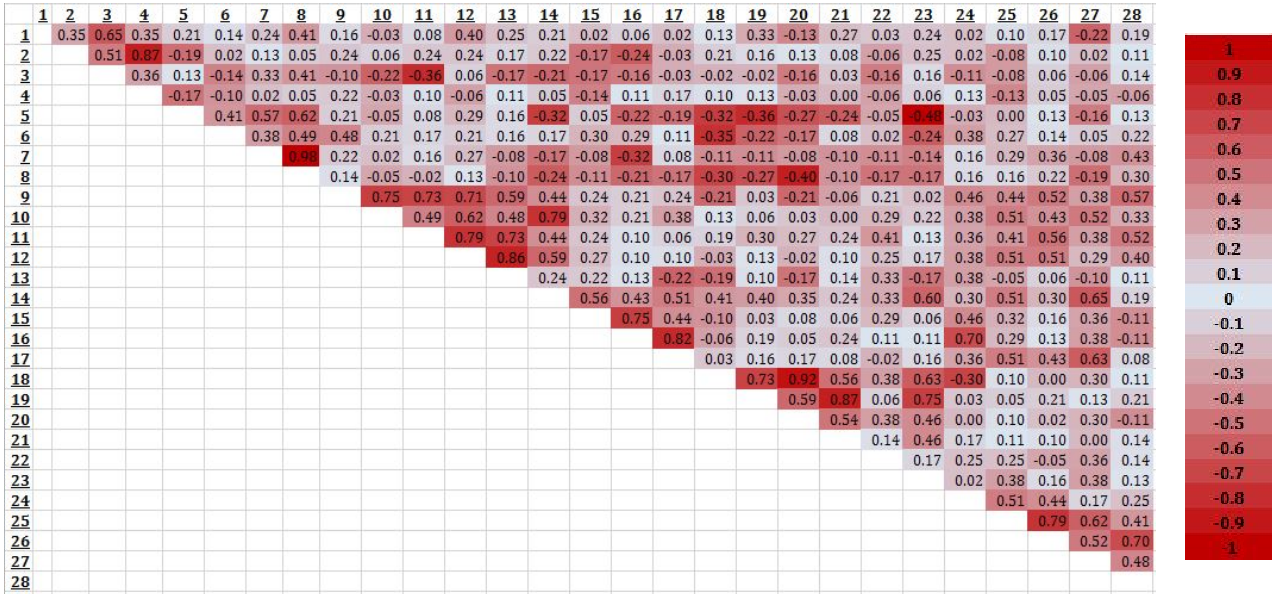


Figure 4.2. Position of sources (red circles) and detectors (detectors) for a) prefrontal; b) primary motor; and c) cerebellum areas. Black lines represent channels.



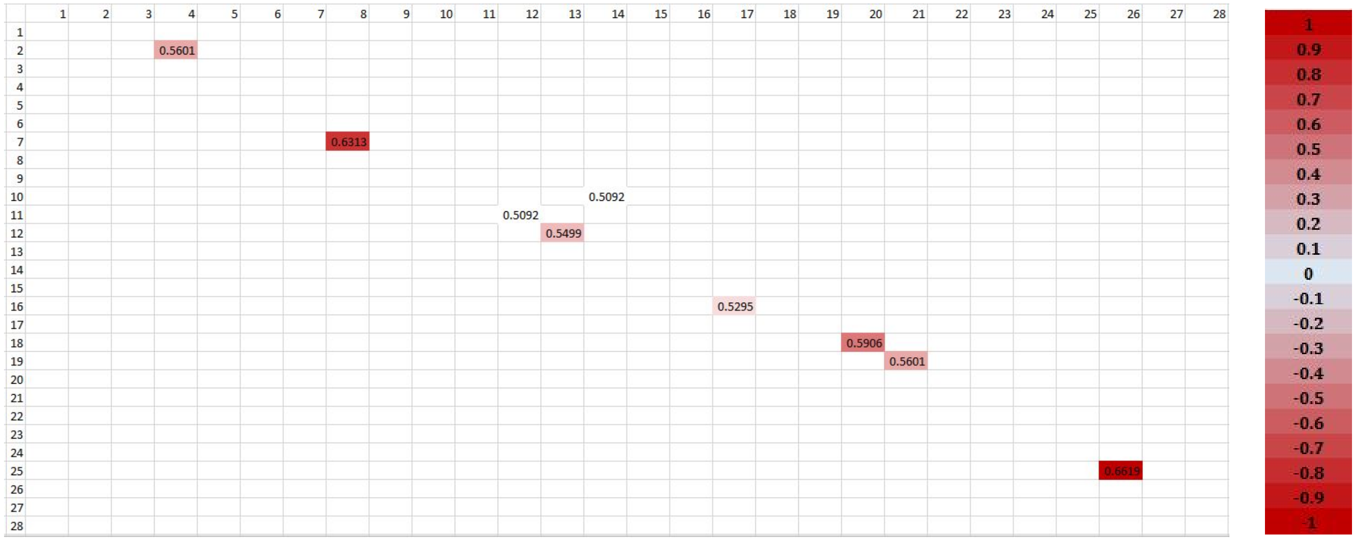
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
1		0.22	0.42	0.22	0.13	0.09	0.15	0.26	0.10	-0.02	0.05	0.25	0.16	0.13	0.01	0.04	0.01	0.08	0.21	-0.08	0.17	0.02	0.15	0.01	0.06	0.11	-0.14	0.12
2			0.33	0.56	-0.12	0.01	0.08	0.03	0.15	0.04	0.15	0.15	0.11	0.14	-0.11	-0.15	-0.02	0.13	0.10	0.08	0.05	-0.04	0.16	0.01	-0.05	0.06	0.01	0.07
3				0.23	0.08	-0.09	0.21	0.26	-0.06	-0.14	-0.23	0.04	-0.11	-0.13	-0.11	-0.10	-0.02	-0.01	-0.01	-0.10	0.02	-0.10	0.10	-0.07	-0.05	0.04	-0.04	0.09
4					-0.11	-0.06	0.01	0.03	0.14	-0.02	0.06	-0.04	0.07	0.03	-0.09	0.07	0.11	0.06	0.08	-0.02	0.00	-0.04	0.04	0.08	-0.08	0.03	-0.03	-0.04
5						0.26	0.37	0.40	0.13	-0.03	0.05	0.18	0.10	-0.20	0.03	-0.14	-0.12	-0.20	-0.23	-0.17	-0.15	-0.03	-0.31	-0.02	0.00	0.08	-0.10	0.08
6							0.24	0.32	0.31	0.13	0.11	0.13	0.10	0.11	0.19	0.18	0.07	-0.22	-0.14	-0.11	0.05	0.01	-0.15	0.24	0.17	0.09	0.03	0.14
7								0.63	0.14	0.01	0.10	0.17	-0.05	-0.11	-0.05	-0.20	0.05	-0.07	-0.07	-0.05	-0.06	-0.07	-0.09	0.10	0.18	0.23	-0.05	0.27
8									0.09	-0.03	-0.01	0.08	-0.06	-0.15	-0.07	-0.13	-0.11	-0.19	-0.17	-0.25	-0.06	-0.11	-0.11	0.10	0.10	0.14	-0.12	0.19
9										0.48	0.47	0.46	0.38	0.29	0.15	0.13	0.15	-0.13	0.02	-0.13	-0.04	0.13	0.01	0.30	0.29	0.34	0.24	0.37
10											0.32	0.40	0.31	0.51	0.20	0.13	0.24	0.08	0.04	0.02	0.00	0.18	0.14	0.24	0.33	0.27	0.34	0.21
11												0.51	0.47	0.29	0.15	0.06	0.04	0.12	0.19	0.17	0.15	0.26	0.08	0.23	0.26	0.36	0.24	0.34
12													0.55	0.38	0.17	0.06	0.06	-0.02	0.08	-0.01	0.06	0.16	0.11	0.24	0.33	0.33	0.18	0.25
13														0.15	0.14	0.08	-0.14	-0.12	0.06	-0.11	0.09	0.21	-0.11	0.24	-0.03	0.04	-0.06	0.07
14															0.36	0.27	0.33	0.26	0.25	0.22	0.15	0.21	0.39	0.19	0.33	0.19	0.42	0.12
15																0.48	0.29	-0.06	0.02	0.05	0.04	0.18	0.04	0.30	0.20	0.10	0.23	-0.07
16																	0.53	-0.04	0.12	0.03	0.15	0.07	0.07	0.45	0.18	0.08	0.24	-0.07
17																		0.02	0.10	0.11	0.05	-0.01	0.10	0.23	0.33	0.27	0.41	0.05
18																			0.47	0.59	0.36	0.24	0.41	-0.19	0.06	0.00	0.19	0.07
19																				0.38	0.56	0.04	0.48	0.02	0.03	0.13	0.08	0.13
20																					0.35	0.24	0.30	0.00	0.06	0.01	0.19	-0.07
21																						0.09	0.30	0.11	0.07	0.06	0.00	0.09
22																							0.11	0.16	0.16	-0.03	0.23	0.09
23																								0.01	0.24	0.10	0.24	0.08
24																									0.33	0.29	0.11	0.16
25																										0.66	0.40	0.26
26																											0.34	0.45
27																												0.31
28																												

Figure 4.3. Correlation values (*r*) between all pairs of channels for younger infants during the unstructured play condition. Darker red values indicate stronger correlations.



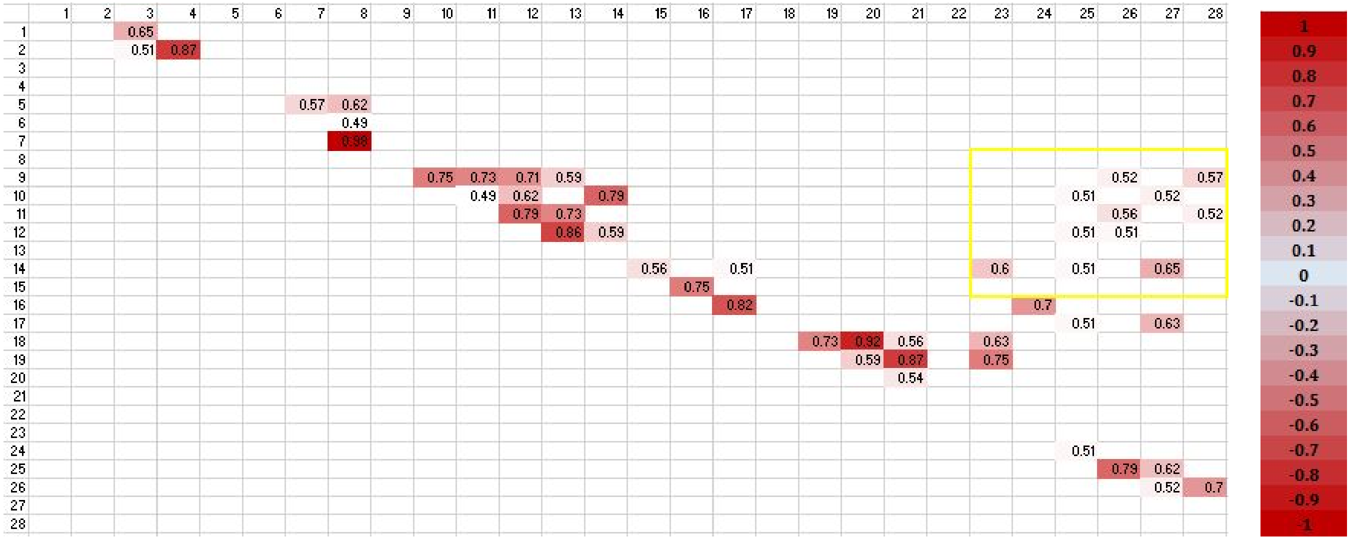
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1		0.35	0.65	0.35	0.21	0.14	0.24	0.41	0.16	-0.03	0.08	0.40	0.25	0.21	0.02	0.06	0.02	0.13	0.33	-0.13	0.27	0.03	0.24	0.02	0.10	0.17	-0.22	0.19
2			0.51	0.87	-0.19	0.02	0.13	0.05	0.24	0.06	0.24	0.24	0.17	0.22	-0.17	-0.24	-0.03	0.21	0.16	0.13	0.08	-0.06	0.25	0.02	-0.08	0.10	0.02	0.11
3				0.36	0.13	-0.14	0.33	0.41	-0.10	-0.22	-0.36	0.06	-0.17	-0.21	-0.17	-0.16	-0.03	-0.02	-0.02	-0.16	0.03	-0.16	0.16	-0.11	-0.08	0.06	-0.06	0.14
4					-0.17	-0.10	0.02	0.05	0.22	-0.03	0.10	-0.06	0.11	0.05	-0.14	0.11	0.17	0.10	0.13	-0.03	0.00	-0.06	0.06	0.13	-0.13	0.05	-0.05	-0.06
5						0.41	0.57	0.62	0.21	-0.05	0.08	0.29	0.16	-0.32	0.05	-0.22	-0.19	-0.32	-0.36	-0.27	-0.24	-0.05	-0.48	-0.03	0.00	0.13	-0.16	0.13
6							0.38	0.49	0.48	0.21	0.17	0.21	0.16	0.17	0.30	0.29	0.11	-0.35	-0.22	-0.17	0.08	0.02	-0.24	0.38	0.27	0.14	0.05	0.22
7								0.98	0.22	0.02	0.16	0.27	-0.08	-0.17	-0.08	-0.32	0.08	-0.11	-0.11	-0.08	-0.10	-0.11	-0.14	0.16	0.29	0.36	-0.08	0.43
8									0.14	-0.05	-0.02	0.13	-0.10	-0.24	-0.11	-0.21	-0.17	-0.30	-0.27	-0.40	-0.10	-0.17	-0.17	0.16	0.16	0.22	-0.19	0.30
9										0.75	0.73	0.71	0.59	0.44	0.24	0.21	0.24	-0.21	0.03	-0.21	-0.06	0.21	0.02	0.46	0.44	0.52	0.38	0.57
10											0.49	0.62	0.48	0.79	0.32	0.21	0.38	0.13	0.06	0.03	0.00	0.29	0.22	0.38	0.51	0.43	0.52	0.33
11												0.79	0.73	0.44	0.24	0.10	0.06	0.19	0.30	0.27	0.24	0.41	0.13	0.36	0.41	0.56	0.38	0.52
12													0.86	0.59	0.27	0.10	0.10	-0.03	0.13	-0.02	0.10	0.25	0.17	0.38	0.51	0.51	0.29	0.40
13														0.24	0.22	0.13	-0.22	-0.19	0.10	-0.17	0.14	0.33	-0.17	0.38	-0.05	0.06	-0.10	0.11
14															0.56	0.43	0.51	0.41	0.40	0.35	0.24	0.33	0.60	0.30	0.51	0.30	0.65	0.19
15																0.75	0.44	-0.10	0.03	0.08	0.06	0.29	0.06	0.46	0.32	0.16	0.36	-0.11
16																	0.82	-0.06	0.19	0.05	0.24	0.11	0.11	0.70	0.29	0.13	0.38	-0.11
17																		0.03	0.16	0.17	0.08	-0.02	0.16	0.36	0.51	0.43	0.63	0.08
18																			0.73	0.92	0.56	0.38	0.63	-0.30	0.10	0.00	0.30	0.11
19																				0.59	0.87	0.06	0.75	0.03	0.05	0.21	0.13	0.21
20																					0.54	0.38	0.46	0.00	0.10	0.02	0.30	-0.11
21																						0.14	0.46	0.17	0.11	0.10	0.00	0.14
22																							0.17	0.25	0.25	-0.05	0.36	0.14
23																								0.02	0.38	0.16	0.38	0.13
24																									0.51	0.44	0.17	0.25
25																										0.79	0.62	0.41
26																											0.52	0.70
27																												0.48
28																												

Figure 4.4. Correlation values (*r*) between all pairs of channels for older infants during the unstructured play condition. Darker red values indicate stronger correlations.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1																												
2				0.5601																								
3																												
4																												
5																												
6																												
7								0.6313																				
8																												
9																												
10														0.5092														
11												0.5092																
12													0.5499															
13																												
14																												
15																												
16																	0.5295											
17																												
18																				0.5906								
19																					0.5601							
20																												
21																												
22																												
23																												
24																												
25																										0.6619		
26																												
27																												
28																												

Figure 4.5. Pairs of channels showing significant correlation values (*r*) based critical values for younger infants during the unstructured play condition. Darker red values indicate stronger correlations.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1			0.65																									
2			0.51	0.87																								
3																												
4																												
5							0.57	0.62																				
6								0.49																				
7								0.98																				
8																												
9										0.75	0.73	0.71	0.59													0.52		0.57
10											0.49	0.62		0.79											0.51		0.52	
11												0.79	0.73													0.56		0.52
12													0.86	0.59											0.51	0.51		
13																												
14															0.56		0.51						0.6		0.51		0.65	
15																0.75												
16																	0.82							0.7				
17																									0.51		0.63	
18																			0.73	0.92	0.56		0.63					
19																				0.59	0.87		0.75					
20																					0.54							
21																												
22																												
23																												
24																									0.51			
25																										0.79	0.62	
26																											0.52	0.7
27																												
28																												

Figure 4.6. Pairs of channels showing significant correlation values (*r*) based critical values for older infants during the unstructured play condition. Yellow box highlights inter-brain regions. Darker red values indicate stronger correlations.

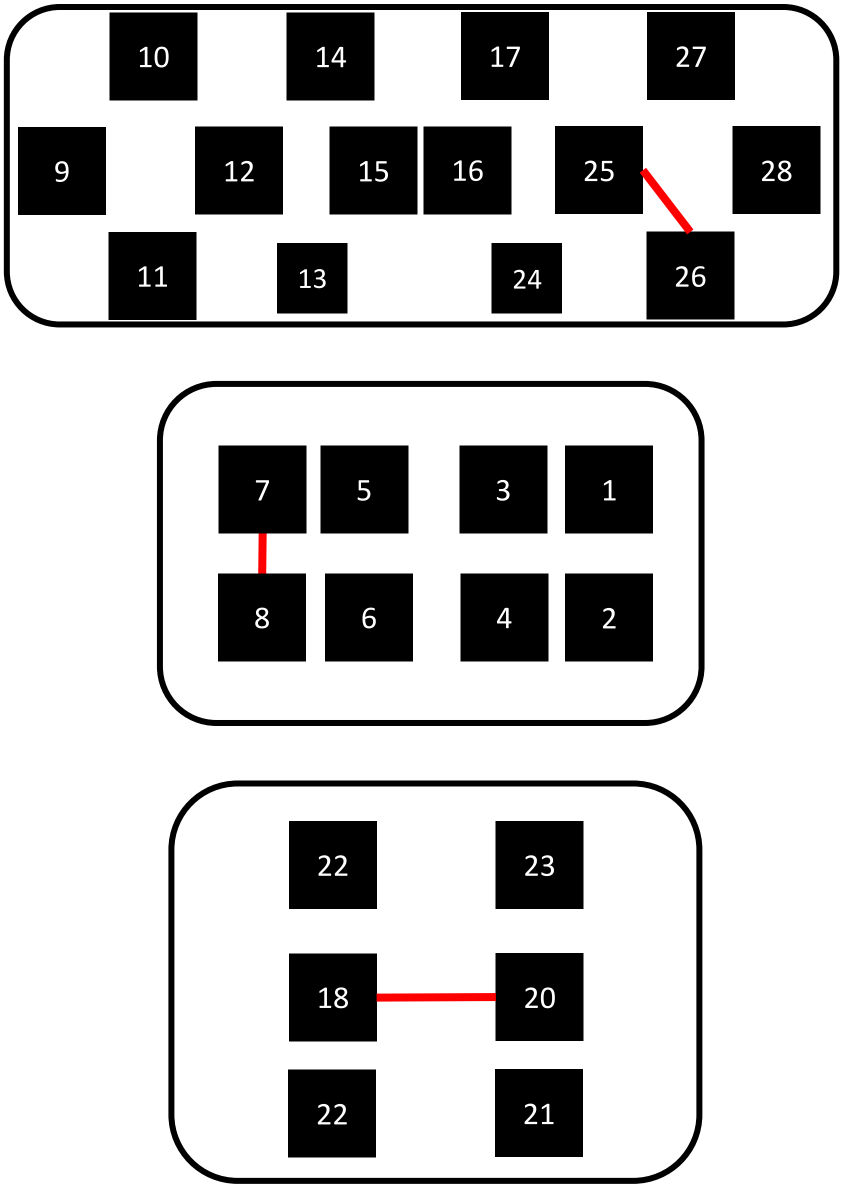


Figure 4.7. Depiction of significant channel pairs (red line, *P* < .05) that were higher in older infants compared to younger infants.

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Chapter V: General Discussion

5.1 Overall Discussion

The series of studies in this dissertation are among the first to directly measure the changes in neural activity that underlie the development of functional motor control early in life. The studies, particularly those from Chapter 3 and 4, were hypothesized based on previous empirical data of kinematic, kinetic, and overt behavioral changes. The data from both studies improve our understanding regarding the dynamic and complex development of neuromotor control.

The studies from Chapter 3 and 4 were hypothesized based on the theory of neuronal group selection (TNGS, Edelman, 1987; Sporns & Edelman, 1993), and the dynamic systems approach. The findings from my studies have directly tested the hypotheses regarding the neural changes as infants improve their motor control. TNGS postulates that the brain has repertoires of circuits that form neuronal groups, or population of interconnected neurons, that share functional properties. These neuronal groups are selected based on the match between the internal and environment constraints compared to the other competing groups. As infants repeat or practice motor skills, similar constraints are matched, thus the same neuronal groups are selected and eventually form a map that is specific and unique to the motor skill (Sporns & Edelman, 1993). This work was supported by studies with cats and the development of their visual cortices (Gray & Singer, 1989), as well as computer simulations (Reeke Jr, Sporns, & Edelman, 1990); but has not been tested with human infants.

The data from Chapter 4 further supports the classical work by Edelman and colleagues. I have successfully utilized fNIRS to take the first step to describing the typical changes in neural activation patterns as infants develop, acquire, and improve functional motor control. Additionally, the data from this dissertation support the host of data that show emergent muscle activity and joint movement patterns as infants increase their experience with a functional motor skill. With the addition of neural data, motor developmental researchers can begin to test hypotheses centered upon the development of the central nervous system. Such research would provide a window into typical and atypical development across many subsystems.

Over the recent years, the use of fNIRS has enabled researchers to understand the functionality of the prefrontal cortex during infancy (Grossmann, 2013). In Chapter 4, the functional activation of the prefrontal cortex during both reaching and stepping tasks demonstrate that infants are actively engaged during goal-directed behavior and that reaching or stepping is not reflexive. To the best of my knowledge, the work presented in Chapter 4 is one of the first attempts to quantify cerebellar activity using fNIRS. Our optode positions were guided by previous EEG and transcranial magnetic stimulation (TMS) studies that used anatomical landmarks that have been shown to detect cerebellar activity (Schutter & van Honk, 2006). However, future research should register optode location with anatomical imaging to confirm the suitability of EEG and TMS localization methods for use with fNIRS.

5.2 Limitations

The series of studies in my dissertation have yielded findings that support the utility of fNIRS during infant movements. However, several issues must be addressed and resolved in future work. First, as discussed above, we did not use subject or group-specific MR images to co-register and localize the positions of the fNIRS optodes. We relied on the work of Okamoto and colleagues (2004) that identified the hypothesized brain areas according to the landmarks of the international 10-20 international system (Jasper, 1958). Most studies, to date, have relied on this method to position the fNIRS optodes. Based on our results with adults, we were able to show that our array of channels covered the primary motor cortex (Nishiyori, Bisconti, & Ulrich, 2016). These results provided insight when we constructed the array of channels for our study with infants (Nishiyori, Bisconti, Meehan, & Ulrich, 2016). To date, studies that have registered fNIRS optodes on infant MR images is scarce, although significant progress has been made over the past few years (Emberson, Richards, & Aslin, 2015; Lloyd-Fox et al., 2014). The use of anatomical registration and photon migration would confirm the exact neuroanatomical location of our measurements.

Second, infants' neuroanatomy undergoes drastic changes over the first year after birth. For example, longitudinal studies examining the neuroanatomical structural changes have shown that an increase in cortical surface area develops at a more rapid rate during the first postnatal year, compared to the second postnatal year (Li et al., 2014). In addition, brain volume and skull thickness increase over the first year of life as well. The changes in these tissues may confound our functional results by altering the absorption rate of light independent of the brain's hemodynamic responses. Further, we kept the same distance between optodes and maintained the same probe geometry. Therefore, we could be quantifying from slightly different regions of the brain across participants and age groups. If the increase in brain volume and skull thickness affected our results, we should have seen similar patterns of change in the area of brain activity between younger and older infants during both functional tasks. The results between younger and older infants during reaching and stepping show a different pattern. For reaching, the area of activity decreased, while for stepping the area of activity increased. Although I cannot completely rule out the affect of increase in brain volume and skull thickness, the results from Chapters 3 and 4 demonstrate that my probe geometry minimized the possible confound attributed to increase in brain volume and skull thickness between the two age groups.

Third, the study from Chapter 4 is the first to quantify hemodynamic activity of the cerebellum in infants using fNIRS. We followed anatomical landmarks from a modified 10-20 international system used in a study with transcranial magnetic stimulation (TMS) in adults, that successfully recorded electrophysiological responses from the human cerebellum (Schutter & van Honk, 2006). We positioned our probe array to surround these areas to quantify cerebellum activity. However, in order to be completely conclusive that our responses were in fact from the infant cerebellum, future work needs to be co-registered and localized to an infant's structural MRI. Moreover, sensitivity distributions of photon migration (Monte Carlo simulations) should be estimated in order to confirm that our probe geometry is accurately measuring Crbl activity.

Finally, the studies in this dissertation did not quantify any behavioral measures that could be acquired during fNIRS data collection, such as limb trajectories and velocities or muscle activation patterns. Indeed incorporating the additional measures would provide more improved measures and analyses. However, the additional equipment and set up time could increase the likelihood of infants becoming fussy and result in fewer successful trials or incomplete protocols. Instead of assessing the behavior on a trial by trial basis, I used the Bayley Scales of Infant Development – Motor subscale This assessment has been a popular tool among motor development researchers and is used to characterize the status of motor development in infants. I used this assessment of motor development to infer experience and skill level for 6 and 12-month old infants, which provided the necessary information for these studies. As the technology improves, future researchers may be in better positions to incorporate additional measures.

5.3 Future Directions

The studies in my dissertation are the first to document the neural activation patterns as infants performed dynamic and functional motor skills. Thus, there are a wide variety of future directions for this line of work. Foremost, longitudinal studies that examine the developing and fluctuating changes in neural activation patterns over the course of developmental time would provide an understanding of how the onset of different skills change the organization and reorganization of the brain. For example, researchers have documented the developmental shifts in early goal-directed hand use and its link to the emergence of postural control and locomotion. Specifically, bimanual reaching declines while there is an increase in unimanual reaching around the time of onset of independent sitting as well as hands and knees crawling (bimanaual onset). Neural activation patterns when infants shift from one pattern of movement to another would provide insight on the plasticity of the developing CNS. Understanding the plasticity of the typically developing CNS is a critical step to describe how the brain changes in infants with disabilities. Such work would enable clinicians to test the impact of interventions and therapies on the developing brain.

Conclusion

This dissertation provided a critical first step to describe the early neural activation patterns that emerge as infants develop and improve their functional motor skills. In other words, this is only the beginning. With the use of fNIRS in the context of dynamic and functional movements in infants, I have shown the successful measurement of three different brain regions in infants related to motor control and learning. Furthermore, the findings support that as infants explore their environment by reaching for toys or traversing across space and improve these behaviors by repeated daily attempts and continuous cycles of perception and action, the underlying neural activity emerges and refines in parallel to the motor outcomes. As I have constructed a portion of the necessary groundwork, future research can further build, improve, and refine our understanding the development of the central nervous system early in life.

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