EEG During Pedaling: Brain Activity During a Locomotion-Like Task in Humans

Sanket G. Jain
Marquette University

EEG DURING PEDALING: BRAIN ACTIVITY DURING A LOCOMOTION-LIKE TASK IN HUMANS

by

Sanket G. Jain, B.S.

**A Thesis submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for
the Degree of Master of Science**

Milwaukee, Wisconsin

December 2009

ABSTRACT

EEG DURING PEDALING: BRAIN ACTIVITY
DURING A LOCOMOTION-LIKE TASK
IN HUMANS

Sanket G. Jain, B.S.

Marquette University, 2009

This study characterized the brain electrical activity during pedaling, a locomotor-like task, in humans. We postulated that phasic brain activity would be associated with active pedaling, consistent with a cortical role in locomotor tasks. 64 channels of electroencephalogram (EEG) and 10 channels of electromyogram (EMG) data were recorded from 10 neurologically-intact volunteers while they performed active and passive (no effort) pedaling on a custom-designed stationary bicycle. Ensemble average waveforms, two dimensional topographic maps and amplitude of the β (13-35 Hz) frequency band were analyzed and compared between active and passive trials. The absolute amplitude (peak positive-peak negative) of the EEG waveform recorded at the Cz electrode tended to be higher in the passive than the active trials *(paired t-test; $p<0.01$)*. Average power of the center β-band frequency (20-25 Hz) in the active pedaling was significantly smaller than passive pedaling *(Univariate ANOVA; $p<0.01$)*, consistent with β desynchronization. A significant negative correlation was observed between the ensemble average EEG waveform for active trials and the composite EMG (summated EMG from both limbs for each muscle) of the rectus femoris *($r = -0.77$, $p<0.01$)* the medial hamstrings *($r = -0.85$, $p<0.01$)* and the tibialis anterior ($r = -0.70$, $p <0.01$) muscles. These results demonstrated that substantial sensorimotor processing occurs in the brain during pedaling in humans. Further, cortical activity seemed to be greatest during recruitment of the muscles critical for transitioning the legs from flexion to extension and *vice versa*. This is the first known study demonstrating the feasibility of EEG recording during pedaling, and owing to similarities between pedaling and bipedal walking, may provide valuable insight into brain activity during locomotion in humans.

ACKNOWLEDGMENTS

Sanket G. Jain, B.S.

I would like to acknowledge my funding source, The Falk Medical Research Trust. This study was conducted at the Neuromechanics Laboratory and Neural Control of Movement Laboratory at Marquette University.

I would like to thank, Dr. Brian Schmit for giving me an opportunity to perform my thesis and guiding me throughout my academic career at Marquette University. I appreciate the time you spent for answering my questions. Your insights for my thesis project have been truly invaluable.

I would like to thank, Dr. Sheila Schindler-Ivens for her guidance and allowing me to perform my experiments in her laboratory. I would also like to thank, Dr. Kristina Ropella for serving on my thesis committee and helping me with her ideas.

I would like to thank, Dr. Krishnaj Gourab, Ryan McKindles, Tanya Onushko and Jon Weiser for their support throughout my project. A special thanks to Prajakta Sukerkar for helping me to edit my thesis. I would like to dedicate this thesis to my family who have provided me with support and encouragement all throughout my life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

1.1 Neural Control of Locomotion

The neural control of locomotion occurs via the combined action of the peripheral afferents (Grillner et al. 1978; Duysens et al. 1980; Andersson et al. 1983; Pearson et al. 1992), spinal locomotor centers (Sherrington 1910; Brown 1911) and supraspinal networks (Eidelberg et al. 1981; Jahn et al. 2008). Particularly in humans, the role of supraspinal regions in locomotion is not well established compared to other neural structures like the peripheral afferents and spinal cord networks. The role of the motor cortex during locomotion, particularly, is still a topic of much debate. Therefore, the purpose of this thesis is to investigate the role of the human cortex during a locomotor-type task. Our approach involved the use of electroencephalography (EEG) as an imaging modality for recording the cortical activity during a pedaling task. This chapter will review the relative contribution of the peripheral afferents, spinal cord networks and supraspinal control of locomotion in humans and animals. Furthermore, this chapter will discuss EEG as an imaging modality.

1.1.1 Spinal Control of Locomotion

Previous studies involving spinal-transected cats have shown that neural circuits in the spinal cord are capable of producing alternate rhythmic flexion-extension movements in the hind limbs in the absence of supraspinal control or phasic afferent feedback (Sherrington 1910; Brown 1911). These neural circuits, termed as the ‘Central Pattern Generators’ (CPG), are located within the lumbosacral spinal cord and are responsible for coordinating basic rhythmic movements during walking and swimming in

animals (Pearson 1993). Although CPG are capable of producing basic locomotor patterns, it must be emphasized that the CPG alone cannot be responsible for accurate control of locomotion in animals. For example, Drew et al. demonstrated that cats with bilateral lesions of the dorsolateral funiculi and dorsal columns, unlike the controls, were unable to modify their gait pattern in order to overcome obstacles during treadmill walking, suggesting the role of supraspinal inputs during gait modifications (Drew et al. 2002).

Observations of rhythmic movements in human spinal cord injury (SCI) subjects (complete and incomplete) indicate the existence of similar CPG networks in humans. For example, a subject with complete spinal cord lesions produces rhythmic contractions of the trunk and lower limb muscles (Bussel et al. 1988; Bussel et al. 1996). Peripheral stimulation of the flexor reflex afferents modulate these rhythmic movements in the subject. Also, electrical stimulation of the spinal cord close to the L2-L3 segments in patients with complete SCI evokes rhythmic flexion-extension patterns in the legs (Rosenfeld et al. 1995; Dimitrijevic et al. 1998; Shapkova et al. 2001). In incomplete SCI subjects, similar involuntary flexion-extension movements have been observed while they were undergoing treadmill training. These cyclical movements are reported when the subjects are in supine position with extended hips indicating the existence of human CPG (Calancie et al. 1994; Dobkin et al. 1995).

However, unlike animals, human CPG alone do not produce basic locomotor patterns. Supraspinal inputs are necessary to activate the CPG networks. Thus, attempts at rehabilitating incomplete spinal cord lesion patients by treadmill training shows functional recovery of gait, which is absent in patients with a complete spinal cord lesion

(Wernig et al. 1995; Barbeau et al. 2001). Moreover, functional deficits in locomotion due to lesions in cortical areas or pyramidal tracts are greater in humans compared to those in animals (Porter et al. 1993). Also, peripheral load afferents modulate muscle recruitment during walking in normal (Sinkjaer et al. 2000; Dietz et al. 2002), SCI (Dietz et al. 2002; Lünenburger et al. 2006; Duysens et al. 1995; Harkema et al. 1997; Gordon et al. 2009) and infant (Yang et al. 1998a) subjects. These support the understanding that CPG networks in humans do not function independently but rely more on the peripheral afferents and the supraspinal networks than in other animals. The next sections provide more insights about role of peripheral and supraspinal inputs.

1.1.2 Peripheral Afferent Control of Locomotion

Peripheral afferents from muscles provide sensory feedback to the CPG during locomotion in lower animals. CPG use this sensory information to time and shape different phases of muscle activity during the gait cycle. There are two major types of locomotor-related sensory inputs that can activate, block or regulate the output of the CPG. The first sensory input is the load receptor input from proprioceptive afferents in the ankle muscles and the second sensory input originates from the afferents near the hip joint (Pearson 1995; Whelan et al. 1995; Whelan 1996). For instance, positive sensory feedback from ankle extensors in chronic spinalized (Pearson et al. 1992) and decerebrated (Duysens et al. 1980) cats was found to regulate the length of the stance phase while maintaining a constant swing phase during changes in stepping frequency. During the late stance period, a decrease of positive feedback from the unloading of the ankle joint initiates the swing phase (Whelan et al. 1995; Whelan et al. 1997). Along with

ankle extensors, sensory signals from the flexor muscles near the hip are also responsible for initiating the transition from stance to swing in chronic spinalized cats (Grillner et al. 1978; Andersson et al. 1983; Andersson et al. 1981). Hip afferents also provide cues for producing rhythmic muscle activity at different frequencies. Studies in spinalized and decerebrate cats have demonstrated the entrainment of motor patterns to the frequency of the movement applied at the hip joint (Andersson et al. 1983; Andersson et al. 1981; Kriellaars et al. 1994). The mechanisms concerning swing to stance transition are less understood, but some studies indicate sensory signals play a role in this transition as well (Lam et al. 2001; McVea et al. 2005; Stecina et al. 2005). Although the CPG in the spinal cords of animals could produce locomotor activity independently, sensory feedback from receptors in the joints and muscles helps to bring sudden modification in the gait pattern to compensate for disturbances during locomotion (Reviews by (McCrea 2001; Rossignol et al. 2006)).

There are substantial similarities between the role of sensory inputs in locomotion of humans and lower animals (Duysens et al. 2000; Pang et al. 2000; Donelan et al. 2004). Therefore, even in humans, afferent activity is required to shape the ongoing locomotor pattern and control phase transitions. For instance, a study by Sinkjaer et al. involved unloading the ankle extensors at different times during the stance phase in humans. They observed decreased activity in the tibial nerve afferents during the unloading of ankle extensors (Sinkjaer et al. 2000), similar to what was found in cat studies. Apart from this similarity, unlike the role of group Ib afferents in cats (Conway et al. 1987), it is still unclear whether group Ib or group II afferents are responsible for sensory feedback in humans (Sinkjaer et al. 2000; Stephens et al. 1996; Faist et al. 2006).

Also, sensory feedback from ankle load afferents has been shown to increase hip extension during gait in both normal and SCI subjects (Gordon et al. 2009). Similarly, hip flexion can be enhanced in SCI subjects by unloading the ankle planterflexor muscles following hip extension (Wu et al. 2006). These studies indicate an involvement of the sensory feedback from the ankle muscles towards the generation of locomotion pattern in humans. Hip position is also responsible for stance to swing transition. During an infant study it has been observed that as the hip is extended, the stance phase is completed and the swing phase is initiated (Pang et al. 2000). This shows the contribution of hip afferents for phase transitions in humans. Such sensory feedback mechanisms can also be used to design rehabilitation techniques that could directly modulate the CPG and improve walking in subjects with impaired locomotion.

1.1.3 Supraspinal Control of Locomotion

The role of supraspinal networks is documented for maintaining accurate limb placement in response to obstacles and unexpected perturbations during locomotion in lower animals (Amos et al. 1987; Amos et al. 1989). For instance, descending commands from the motor cortex in cats are responsible for changes in limb trajectory and accurate paw placement that is required for stepping over obstacles on the treadmill (Beloozerova et al. 1993; Armstrong et al. 1996; Kably et al. 1998). Another study by McVea in cats claimed the forebrain to be responsible for long-term (>24 hours) aftereffects developed after repetitive presentation of obstacles (McVea et al. 2007). The aftereffect was an increase in step height of the hind limb even when no obstacles were present. However, they found that decerebrated cats demonstrated virtually no learning aftereffects (<1

min), thereby indicating the role of supraspinal structures in developing long-term modifications of locomotion. The corticospinal system is also reported to be important for precise modification of the hind-limb trajectory in cats. The loss of corticospinal input in cats due to lesions in the corticospinal pathways leads to an inability to overcome obstacles (Drew et al. 2002). Furthermore, experiments involving the control of visually-guided locomotion indicate a contribution of the posterior parietal cortex (PPC) during forelimb placement in cats (Lajoie et al. 2007b). This claim is supported by another study where lesions in the PPC of cats causes a disruption of the forelimb-hindlimb coordination and eventually leads to a failure to overcome obstacles (Lajoie et al. 2007a).

Supraspinal networks provide corrective motor drive in lower animals like cats (Lacquaniti et al. 1984; Jacobs et al. 1996; Matsuyama et al. 2000) and rats (Bolton et al. 2006). This corrective drive maintains stable movements and optimum body posture in unfriendly environments such as inclined surfaces. Experiments in cats have also identified the role of the cerebellum in maintaining equilibrium during locomotion (Armstrong et al. 1984a; Armstrong et al. 1984b). The nucleus fastigial and nucleus interpositus in the cerebellum rhythmically modulate their discharge for maintaining equilibrium during locomotion (Orlovsky 1972). Abnormalities in gait cycle and loss of equilibrium have been reported with lesions near the midline of the cerebellum (Dow et al. 1958; Yu et al. 1983). Along with the cerebellum, the PPC is also involved in maintaining balance during locomotion. Strong projections between these two areas allow both to maintain balance during locomotion simultaneously (Stein et al. 1992; Marple-Horvat et al. 1998; Cerminara et al. 2005).

In humans, there is indirect evidence that shows the involvement of supraspinal networks in locomotor-type tasks that do not require substantial gait modifications. This evidence, however, does not explain the precise role of the structures involved during locomotion. Functional imaging techniques such as single photon emission computed tomography (SPECT) (Fukuyama et al. 1997), positron emission tomography (PET) (Christensen et al. 2000) and near infrared spectroscopy (NIRS) (Miyai et al. 2001; Suzuki et al. 2004) display activation in the sensorimotor areas, cerebellum and the brainstem in response to walking. However, the precise role of these activated regions is unclear. These areas may be involved only during the sensory processing of large afferents signals or the generation of motor outputs or both. In the PET study by Christensen et al., differences between active and passive walking were computed to be localized over the sensorimotor areas, thus indicating the role of the cortex for generating motor commands. Observations in patients with corticospinal tract lesions have led to the understanding that an intact corticospinal tract is necessary for the proper control of locomotion (Nathan 1994). These observations motivated electrophysiological studies using transmagnetic stimulation (TMS) that showed the modulation of corticospinal tract signals during walking on a flat surface (Schubert et al. 1997; Capaday et al. 1999). Another TMS study by Petersen et al. used weak stimuli to activate only the inhibitory cortical interneurons during walking. EMG signals recorded from leg muscles in response to these stimuli were decreased, demonstrating that efferent signals from the cortex regulate locomotion in humans (Petersen et al. 2001). Overall, this indirect evidence identifies the role of human cortex and other supraspinal regions during uncomplicated locomotion.

1.2 Pedaling: An Alternate to Walking Task

Major constraints for performing walking task under experimental conditions are to remain still, achieve stability and balance. As a result, different approaches were considered to avoid problems associated with walking (e.g. inability to walk in an MRI scanner, and maintaining stability and balance to avoid motion artifacts). These include recording brain activity immediately after walking (Fukuyama et al. 1997), during imagined walking (Deutschlander et al. 2009; Bakker et al. 2008; Iseki et al. 2008; Wagner et al. 2008), during movement of a single lower extremity joint (Dobkin et al. 2004; Sahyoun et al. 2004; Ciccarelli et al. 2005) and during pedaling a stationary bicycle (Christensen et al. 2000; Mehta et al. 2009). Among these approaches, pedaling can be considered as a close approximation to performing actual locomotion. Both pedaling and walking are rhythmic and reciprocal movements with almost similar frequencies (Winter 1983; Coast et al. 1985). The timing and intensity of flexion-extension movements of the lower extremity along with the sensory feedback generated during pedaling is comparable to those observed during walking (Brown et al. 1997; Brown et al. 1998; Kautz et al. 1998; Raasch et al. 1997). Furthermore, both tasks demonstrate the same phase-dependent modulation of reflexes (Brown et al. 1993). Pedaling experiments can be performed either unilaterally or bilaterally with good balance. Also, they can be more controlled and manipulated to study changes in neuromuscular functions under different loads and speed (Ericson 1988). Thus, pedaling is a practical alternative to study locomotion and its control by different parts of the central nervous system.

1.3 Objective

The objective of this project is to understand the role of the human motor cortex in a simple locomotor-like task. Specifically, by uncovering the differences between active (sensory and motor) and passive (sensory alone) pedaling, we will be able to understand the contribution of the cortex toward performing locomotor-like tasks. Our approach involves the use of EEG as an imaging modality to identify the cortical regions involved in pedaling and also to understand the role of EEG beta frequencies during pedaling. EEG was selected due to its non-invasive nature and its high temporal resolution. To better appreciate the results of this project, it is necessary to have a clear understanding of the EEG and its physiological implications. For this purpose, the next section provides with an overview of the fundamentals of EEG.

1.4 Electroencephalography: Cortical Imaging Modality

Electroencephalography (EEG) belongs to the class of electrophysiological modalities that measure the electrical activity of the brain using scalp electrodes with high temporal resolution (on the order of milliseconds). This is complimentary to other imaging modalities such as fMRI which provide high spatial resolution but relatively low temporal resolution. Since the execution of any sensory or motor activity usually involves fast synchronization of neural processes in different parts of cortical and sub-cortical structures, a high temporal resolution is required to capture these neural events. However, most imaging techniques with high spatial resolution are able to provide an understanding of the areas involved during the performed task but fail to demonstrate the sequence of neural activation due to their relatively poor temporal resolution. Alternatively, due to its

high temporal resolution, EEG can differentiate rapidly occurring neural processes and hence can be used to study the sequence of activations of the underlying neural structures (though with relatively poor spatial resolution). EEG studies can also provide knowledge of the involvement of the various frequency bands like alpha (8-12 Hz) and beta (13-35 Hz) during a motor task. Lately, after the commercialization of high-density EEG systems (128-256 channels), there has been an improvement in the spatial resolution obtained from EEG.

Inhibitory and excitatory inputs to neuronal cells produce electrical currents that sum up to produce scalp recorded EEG signals (Misulis et al. 2003). The currents across the membrane generate secondary ionic currents along the cell membranes in the intra- and extra-cellular space. The portion of these currents that flow through the extracellular space is directly responsible for the generation of local field potentials. Specifically, graded post-synaptic potentials (PSP) of the cell body and large apical dendrites of numerous vertically aligned pyramidal cells in cortical areas produce electrical fields in a radial direction that can be recorded by the EEG amplifier (Lopes da Silva 1991). The PSP's are different from action potentials that travel along the neuron membranes in that they are lower in frequency and amplitude and diffuse over a wider area of the scalp (Toga et al. 2002). As a result, the extracellular EEG represents a summation of neural activity from the underlying sources.

The recorded EEG potentials are highly sensitive and variable in nature. EEG is not only sensitive to small amplitude neural potentials but also to ambient noise and movement artifacts. The strength of the electrical signal at the source, synchronization between the cells firing, orientation of the cells firing, amount of attenuation of the

electrical signal by overlying neural areas, and the contact impedance of the recording electrodes together contribute to the amplitude of the signal recorded on the scalp. These factors along with others are responsible for the highly variable nature of EEG (Toga et al. 2002).

The EEG potentials can be represented as vectors of cortical activity and thus have both a magnitude and a directional component. For instance, if the superficial layer of the cortex has a positive field potential compared to the deeper layers of cortex, then scalp potentials can be represented by a vector from the negative field to positive field. This vector is termed as a 'dipole' in the EEG literature. These dipoles enable us to perform source localization and 2-D topographical mapping from EEG potentials in response to any neural activity.

Rhythmicity is a fundamental property of many neurons and neuronal circuits that are used for the generation of motor, sensory and cognitive activities. The source and span of these EEG rhythms can vary from a single neuron to inter-cortical neural structures depending on the activity being performed (Misulis et al. 2003). EEG rhythms are normally associated with five bands: Delta (DC- 4 Hz), Theta (4-7 Hz), Alpha (8-12 Hz), Beta (13-35 Hz), and Gamma (above 35 Hz). Each of these frequency bands have significance depending upon the nature of the physiological activity (motor, sensory or cognitive) being performed or existence of pathological situations. For our study, we are interested in the beta (β) frequency band.

β band is involved in sensory feedback and motor command processing to execute a desired movement (Pfurtscheller 1981). During initiation and execution of movement, decrease in the power of β frequencies has been observed. This decrease in the power is

restricted to the electrodes overlying the cortical areas corresponding to the moving limb (Jasper et al. 1938; Jasper et al. 1949). This phenomenon is termed as Event-related Desynchronization (ERD). ERD has been previously associated with voluntary movements of hand (Pfurtscheller 1981) and leg (Neuper et al. 1996). After termination of the movements, the power in the β frequencies is recovered to the state before the initiation of movement. This phenomenon is termed as Event-related Synchronization (ERS). ERS has been associated as the rhythms of resting cortex (Pfurtscheller 1992).

1.5 Specific Aim

The specific aim of this study was to determine whether primary sensorimotor cortices are involved in pedaling. To investigate this, we recorded EEG signals from 64 channels during two conditions of pedaling (1) an active condition, and (2) a passive condition. We performed both time and frequency domain analysis on active and passive pedaling conditions. In the time domain, we compared the cortical potentials during active and passive pedaling. In the frequency domain, we subtracted the results from active and passive tasks and tested whether the differences between the two tasks were significant. We also performed correlation analysis between average EEG and average EMG waveform to find relationship between the two signals. We hypothesize the activation of the primary sensorimotor cortices during active and passive pedaling tasks to be significantly different across the two conditions thus demonstrating the role of these cortices in active pedaling.

2 EEG DURING PEDALING: BRAIN ACTIVITY DURING A LOCOMOTION-LIKE TASK IN HUMANS

2.1 Introduction

In humans, the cerebral cortex may play an important role in the control of locomotor function. The role of the cortex may be particularly strong in humans since a unique characteristic of human locomotion, in comparison to other primates, is 'habitual bipedalism with the trunk and head in an erect posture' (reviewed in (Schmitt 2003)). This type of locomotion has provided humans with a distinct evolutionary advantage over other animals by freeing the upper limbs during locomotion, and significantly decreasing the energy cost of walking (Sockol et al. 2007). However, it has also made the task of walking more complex and possibly more dependent on corticospinal function for humans, compared to lower animals (reviewed in (Nielsen 2003)). Consequently, in contrast to lower animals (rats, (Little et al. 1988) cats, (Rossignol et al. 2004) rabbits (Lyalka et al. 2005), and non human primates (Courtine et al. 2005); (Babu et al. 2008), disruption of supraspinal control, as in stroke (Kelly-Hayes et al. 2003) or spinal cord injury (Dobkin et al. 2007), more severely impairs locomotion in humans (reviewed in (Rossignol 2000). Thus, characterization of the cortical contribution to locomotor control in humans is important to understanding the pathophysiology of impaired locomotion after an injury to the central nervous system.

Assessing the cortical contribution to locomotor control in humans is challenging due to difficulties in quantifying brain activity during walking. Walking generates head movement and requires the subject to be erect and moving in space, with minimal constraints. In order to circumvent these problems, brain activity has been recorded

during conditions that differ from actual walking. Approaches have included recording brain activity immediately after walking (Fukuyama et al. 1997), during imagined walking (Deutschlander et al. 2009; Bakker et al. 2008; Iseki et al. 2008; Wagner et al. 2008), during movement of a single lower extremity joint (Dobkin et al. 2004; Sahyoun et al. 2004; Ciccarelli et al. 2005) and during pedaling a stationary bicycle (Christensen et al. 2000; Mehta et al. 2009). Pedaling was used in the current study because it involves actual movement of the legs, which generates sensory feedback, and the reciprocal, cyclical nature of the task is similar to walking.

Previous measurements of brain activity during pedaling have been limited to techniques that are dependent on hemodynamic/metabolic responses, which have restricted the temporal resolution of the data. For example, brain activity has been measured during pedaling using positron emission tomography (PET) (Christensen et al. 2000) and functional magnetic resonance imaging (fMRI) (Mehta et al. 2009), both of which indicate that primary cortical structures are active during pedaling. Since both fMRI and PET are based on hemodynamic/metabolic responses, temporal resolution necessary to ascertain the timing of the brain activity relative to the pedaling cycle is still unknown. High temporal resolution is essential if brain function is to be associated with the patterns of muscle activity during different phases of the pedaling cycle (summarized for walking in cats by (Drew et al. 2002)). Consequently, the use of electroencephalography (EEG) to monitor cortical activity during pedaling is appealing, since EEG is noninvasive and has the capability of high time resolution.

In order to characterize cortical activity during a locomotor-like task, high density (64 channels) EEG measurements were made while ten young healthy adults pedaled a

custom stationary bicycle. We hypothesized that EEG would demonstrate brain activation over anatomically appropriate scalp regions, i.e. over the leg representation area of the sensorimotor cortex, with different patterns of activation during active vs. passive pedaling. Further, a correlation between the EEG activity over these regions of the brain and activity of the leg muscles was expected.

2.2 Methods

2.2.1 Study Participants

Ten young, healthy, neurologically intact subjects (male and female) who were comfortable with pedaling for half an hour participated in this study (age 22 to 32 years, median 26 years). The study protocol was approved by the Institutional Review Board of Marquette University, Milwaukee, Wisconsin. Written informed consent was obtained from all subjects prior to participation in the study.

2.2.2 Pedaling Device

The pedaling device and acquisition of crank position data has been described previously (Schindler-Ivens et al. 2008). Briefly, a custom-designed stationary bicycle with a rigid, reclined backboard was used as the pedaling device (Figure 2.1a). The backboard supported the subject's head and trunk during pedaling, thus reducing movement artifacts in the EEG recordings. Optical encoder (BEI Technologies Inc., Goleta, CA) was used for digitizing the angular position of the cranks. Digital signals from the optical encoder were converted to analog signals using a digital to analog converter before sampling by the main data acquisition computer.

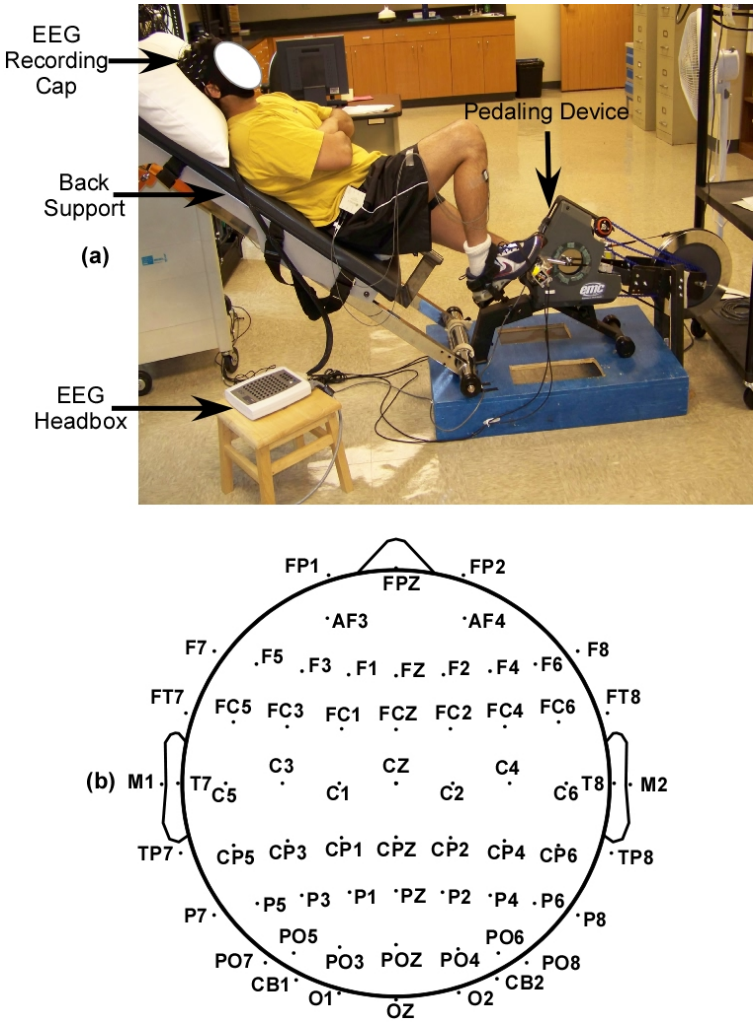

Figure 2.1 Experimental Setup. (a) Subject is seated on the custom designed bicycle. His legs are in the TDC position. (b) Schematic showing the position of the 64 electrodes on the electrode cap (©Compumedics Neuroscan, El Paso TX). The electrodes are shown outside the head to indicate their inferior position w.r.t. the other electrodes lying inside the head.

2.2.3 EEG and EMG Recording Systems

The QuikCap electrode cap (Compumedics Neuroscan, El Paso, TX) was used for EEG electrode placement (Figure 2.1b). The stretchable electrode cap contained 64 sintered Ag-AgCl electrodes arranged according to the modified combinatorial system of electrode placement (American Clinical Neurophysiology Society 2006). The reference electrode was positioned near the vertex between the Cz and CPz electrodes and the

ground electrode was located over the frontal area of the scalp, between the Fz and FPz electrodes. The Ag-AgCl electrodes were located within small receptacles on the scalp side of the cap, which housed sponge-backed felt discs. The electrodes were connected to the EEG amplifier via a headbox, and the headbox was connected to a high input impedance Synamps^{2} amplifier (Compumedics Neuroscan). Before each recording, disposable sponge discs were inserted into electrode receptacles and the QuikCap was secured to the subject's head with a chin strap. The sponge discs were hydrated with about 0.2 ml of a proprietary electrolyte solution (Compumedics Neuroscan) which then expanded to make contact with the scalp. Electrode impedances were decreased and maintained below 10 KΩ. The electrodes were connected to the Synamps^{2} EEG amplifier (Compumedics Neuroscan), which in turn, was connected to a PC for data acquisition.

EMG was recorded bilaterally using bipolar skin electrodes (10 mm length, 1 mm width, 1 cm inter-electrode distance, DelSys, Inc., Boston, MA) from the Soleus (SOL), Vastus Medialis (VM), Tibialis Anterior (TA), Medial Hamstring (MH) and the Rectus Femoris (RF) muscles. EMG signals were pre-amplified 10X at the electrode site. Remote differential amplification at 1000X was done using an EMG amplifier system (DelSys Bagnoli-8 EMG System, DelSys, Inc.) with a common mode rejection ratio of 92 dB and a frequency bandwidth of 20 to 450 Hz. This amplifier was connected to a PC via a 16 bit A/D converter (Micro 1401 mk(II), Cambridge Electronic Design, Cambridge, England) for acquiring the EMG signals.

2.2.4 Experimental Protocol

Subjects were seated on the cushioned seat of the stationary bicycle, with their back reclined on the rigid backboard. The subject's trunk was snugly strapped to the rigid backboard and a sandbag was placed around the head. Each subject participated in two pedaling tasks: active and passive, and both recordings were done during a single experimental session. During pedaling, whenever the crank rotated through the top dead center position of the right leg (TDC; Right leg completely flexed and Left leg completed extended (Raasch et al. 1999), a 5 V pulse was generated by the optical encoder. This pulse was routed to the EEG and EMG recordings to track the start of every pedaling cycle.

(i)Active pedaling

For active trials, subjects were asked to pedal in a forward direction at a comfortable speed. The eyes were closed to minimize eye movements, blink artifacts and to prevent any visual feedback of the pedaling speed and leg position. Subjects were instructed to pedal at a slow, comfortable rate. No effort was made to cue or control the speed of pedaling in order to prevent EEG activity due to cognitive processes associated with matching the pedaling speed to a visual or auditory cue. The average pedaling speed across all subjects was 2.1 s/cycle (±0.5 s/cycle). The resistance to pedaling was kept at minimum for all trials and subjects. The total duration of the active pedaling was 20 minutes. A short break after 10 minutes of pedaling was provided, if required.

(ii)Passive pedaling

For the passive trials, the subject's feet remained strapped to the pedal of the bicycle while the crank was rotated by one of the investigators. The speed of passive

pedaling was matched to the average speed of active pedaling for the subject. The subjects were asked to completely relax and EMG from the leg muscles was monitored to confirm that subjects were not generating muscle activity during pedaling. A single trial of 10 minutes was recorded.

2.2.5 Data Acquisition and Analysis

Continuous EEG, EMG and crank position data were recorded during each trial (Figure 2.2). Continuous EEG data were amplified 2010X, filtered at 0.5 Hz (high pass filter cutoff frequency) to 500 Hz (low pass filter cutoff frequency), digitized at 2000 Hz and recorded on a computer running the Scan 4.3 EEG acquisition/analysis software (Compumedics Neuroscan). Crank position and EMG data were sampled at 2000Hz, digitized by a 16 bit A/D converter (Micro 1401 mk(II), Cambridge Electronic Design) and acquired on a PC running Spike 2.0 software (Cambridge Electronic Design).

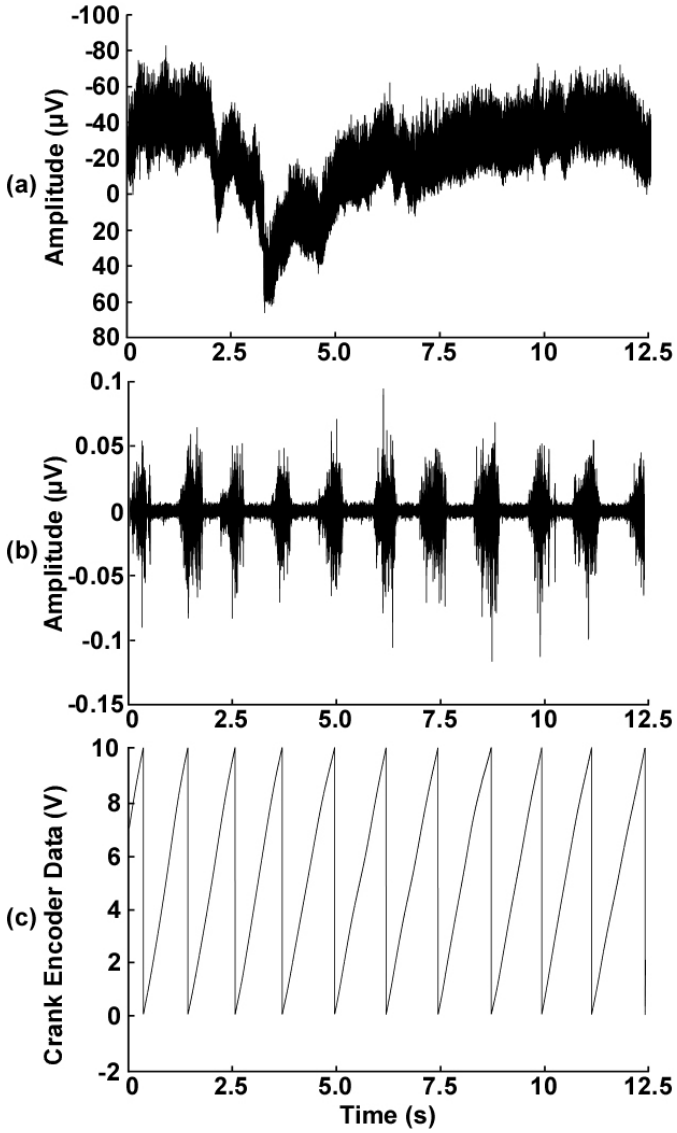

Figure 2.2 Data Acquisition. (a) Raw continuous EEG data from one subject recorded at the Cz electrode. (b) Raw continuous EMG data from one subject recorded at left MH muscle. (c) Voltage data recorded from crank encoder representing crank angle during pedaling. Figure 2.2(a-c) illustrates continuous raw data for ~11 pedaling cycles.

A complete dataset for one subject was defined as containing EEG, EMG and crank position data for both the active and passive trials; with at least 140 EEG epochs in each trial. An epoch is the data (EEG or EMG) recorded during a single pedaling cycle. Nineteen sets of data (from 10 active trials and 9 passive trials) fulfilled this criterion, and further analysis was done on these 19 sets. Active pedaling trials had 208 to 773 epochs

(3 subjects had 208 to 327 epochs, 7 subjects had 465 to 773 epochs) and passive pedaling trials had 142 to 381 epochs (1 subject had 142 epochs, 8 subjects had 288 to 381 epochs). Data analysis was done using the EDIT 4.3 EEG analysis software (Compumedics Neuroscan), the EEGLAB toolbox (Delorme et al. 2004) and custom programs written in MATLAB (The Mathworks, Inc., Natick, MA).

Continuous EEG data (.cnt files) were converted into ASCII (.dat files) format for processing. An event file was generated using the EDIT 4.3 software. Timings of each event (each time the right leg reached the TDC position) were used to segregate continuous EEG data into epochs. Each epoch represented EEG activity during one complete pedaling cycle, starting from the TDC position. The TDC position was thus the origin of each epoch (0 ms and 0° position).

Because subjects were allowed to pedal at a comfortable speed, the length of each pedaling cycle and therefore, the EEG epochs, varied within each trial. Assuming that EEG activity was time-locked to the cycling phase; EEG epochs from the same trial were resized to the same length before they were ensemble averaged to obtain an average potential spatiotemporal map for the pedaling cycle. The following algorithm was implemented for resizing the EEG epochs: the mean epoch length was calculated, and epochs with lengths within 0.3 s of the mean were selected for further analysis. This was an arbitrary threshold, but it allowed epochs of almost similar lengths to be considered for analysis (Mean: 89.7% of total epochs recorded; Range: 13/19 > 90% epochs used, 17/19 >70% epochs used). The next step was to resize the selected epochs to one standard length. Three times the length of the longest of the selected epochs was taken as a standard epoch length for the trial, and all epochs were resized to this target length

using the *resample* function in MATLAB. This resulted in the same length for each individual epoch, while preserving the overall morphology of each cycle. Distortion in the morphology of the signal for each cycle was observed for about 50 data points (0.3% of the original length) at the start and end of each epoch. These regions were excluded from further analysis. Ensemble-average waveforms for each trial were calculated using the resized epochs. The *detrend* function in MATLAB was used to correct for slow, baseline shifts in the ensemble averaged waveforms. The averaged waveforms were then re-referenced to the whole head (Lehmann et al. 1980). These ensemble averaged waveforms for single subject were then resized to an arbitrary length (16384 points). The same analysis was performed for every subject and the ensemble averaged waveforms were generated with same length.

Ensemble average waveforms of each active and passive trial were obtained across subjects, generating the group average waveforms for the active and the passive trials. A global linear interpolation algorithm (Neuroscan 2003) was implemented to generate two dimensional topographic maps at specific phases of the pedaling cycle (at peaks of negative and positive deflections, further described in the results section) in the group average waveforms. These topographic maps represented the voltage distribution over the scalp at specific time points across the pedaling cycle.

The frequency content of the EEG signal was analyzed to calculate the β band desynchronization associated with active and passive pedaling. This analysis was performed using the EEGLAB toolbox (Delorme et al. 2004) for MATLAB. Continuous EEG data from each trial were downsampled to 500 Hz and the first 500 s of the data were used for this analysis. Separate topographic maps representing the amplitudes of

frequencies between 6 to 35 Hz were plotted using the *spectopo* function in EEGLAB. This function utilized the *pwelch* (welch periodogram) function from MATLAB which divided the continuous time-domain signal into 8 segments using a Hamming window with 50% overlap to calculate the amplitude at each frequency. Average amplitude at each frequency was calculated across subjects for the active and passive trials. Before averaging, the amplitudes at each frequency were normalized to the range (maximum amplitude recorded for that trial across all 64 channels – minimum amplitude recorded for that trial across all 64 channels) for the trial. Subsequently, the *topoplot* function in EEGLAB was used to calculate interpolated two dimensional topographic maps showing the amplitude of the specified frequency over different regions of the scalp. We expected the group-average frequency topographic maps to show a greater desynchronization in the β band frequencies for the active as compared to the passive trials. Further, we expected the maximum desynchronization to localize near the electrodes representing the leg representation area of the motor cortex (C1, Cz and C2 electrodes).

EMG was analyzed using custom MATLAB programs. Fourth order Butterworth filters at 20 to 450 Hz (band pass) and 58-62 Hz (band stop) were used to filter the EMG signal (*filtfilt* function in MATLAB). The signals were then rectified and enveloped using a 4^{th} order low pass Butterworth filter at 5 Hz.

Due to the proximity of the locations of the right and left leg representation areas of the sensorimotor cortex, we expected the Cz electrode to represent the electrical activity from both the left and the right leg representation areas of the cortex. To explore the relation between EEG activity recorded at this electrode and the leg muscle EMG activity, composite EMG waveforms representing activity of the same muscle from both

legs were generated. EMGs from the same muscle from the left and right legs were added to yield the composite EMG waveform for each muscle. The group-averaged EMG signals from VM, RF, MH and TA muscles were then cross correlated (*xcorr* function in MATLAB) to the group-averaged EEG from all 64 channels. These cross correlation coefficients (not normalized by autocorrelation values) for every muscle were then interpolated on 2-D topographic maps as described previously.

2.2.6 Statistical Analysis

Statistical tests were done for the following measures:

(i) The difference in the amplitude (maximum positive deflection – maximum negative deflection) of the EEG voltage waveform at the Cz electrode (Jahanshahi et al. 1995) for the active versus the passive trials. For each subject, the active and passive trials data were normalized with the mean of the two trials. A paired t-test was done to test for statistical significance and level of significance was fixed at $p < 0.01$.

(ii) The difference in the mean amplitude of the power in the center β band frequencies (20-25 Hz) in active versus passive trials. For this analysis, only the electrodes over the sensorimotor cortex were considered. Specifically, the central row (C3, C1, Cz, C2 and C4), the row anterior to the central row (FC3, FC1, FCz, FC2 and FC4) and the row posterior to the central row (CP3, CP1, CPz, CP2 and CP4) were considered. A univariate ANOVA (Task and Electrode and Task*Electrode as fixed factors, Subject as a random factor) was performed on the mean power values. Also, individual paired t-tests were performed to identify the electrodes with significant

difference between the two tasks. Statistical tests for this section were performed using SPSS. Level of significance was fixed at $p < 0.05$ for this test.

(iii) The correlation between group average composite EMG waveforms for 5 leg muscles (SOL, MG, TA, MH, RF and VM) and the group average EEG voltage waveform at the Cz electrode. Separate normalized correlation coefficients (r) and p values (testing hypothesis of no correlation) were calculated for each muscle using the *corrcoef* function in MATLAB. Level of significance was set at $p < 0.05$ for this test.

2.3 Results

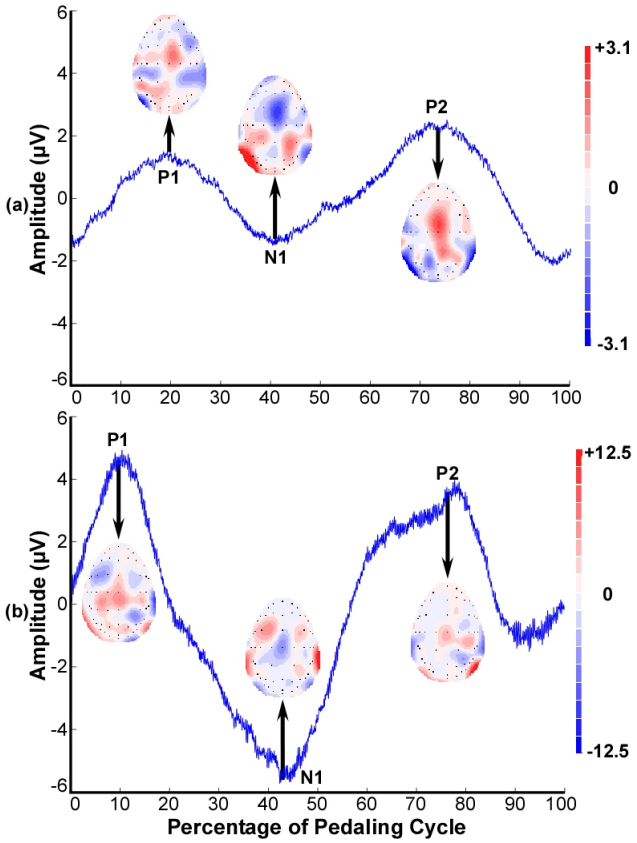

Figure 2.3 Time Domain Results. (a) Group average EEG waveform recorded over the Cz electrode during active pedaling trials. (b) Group average EEG waveform recorded over Cz electrode during passive pedaling trials. The arrows indicate the time within the pedaling cycle when the 2-D topographic maps have been generated. The color map on the right of each trace shows the range of voltage amplitudes. In the 2-D maps, the nose is pointing upwards, left and right ears are on the left and right side respectively. These 2-D maps were generated using Scan 4.3 (©Compumedics Neuroscan, El Paso TX)

The ensemble-averaged EEG waveforms at the Cz electrode demonstrated voltage changes over the motor cortex leg area throughout the pedaling cycle (Figure 2.3). The group averaged waveforms at the Cz electrode for both the active and the passive pedaling trials showed alternate positive and negative potentials, occurring twice during the pedaling cycle. The positive peaks (P1 and P2) occurred around the TDC+90º and TDC+270º marks of the pedaling cycle. The positive peaks were separated by a negative

peak (N1) occurring around the BDC (bottom dead center: right leg down and left leg up, corresponding to the TDC+180º mark) of the pedaling cycle. Another negative peak occurred at approximately the TDC position, but this peak was not analyzed further, as resizing of the epochs led to distortions and rejection of data points at the beginning and end of the EEG waveforms corresponding to the TDC position. The amplitude of the EEG waveform (maximum positive – maximum negative deflection) was significantly greater ($p<0.01$) in passive as compared to active trials in 9 of 9 subjects (Table 2.1). The passive trials were on average 2.2±0.9 (mean ± standard deviation) times greater than the active trials.

Subject	1	2	3	4	5	6	7	8	9	**Mean**	**Std. Dev.**
Active	6.98	14.76	3.02	9.41	9.15	1.27	2.61	12.17	14.36	8.19	5.08
Passive	8.67	21.72	7.52	24.02	18.83	2.92	4.45	14.53	59.49	18.02	17.29

Table 2.1: (EEG Amplitude During Active and Passive Pedaling) Amplitude (μV) recorded at Cz electrode during active and passive pedaling.

Topography of the voltage distribution at P1 and P2 in group-averaged EEG waveforms showed an area of positive potential over the approximate leg representation area of the sensorimotor cortices (Insets in Figures 2.3). Similarly, the voltage topography during at N1 showed an area of negative potential over the same area. The areas of positive and negative voltages were better defined in topographic maps derived from group average waveforms than from any of the individual trials. This suggested that the areas of voltage changes during pedaling were common across all subjects, with preponderant effects over the leg representation area of the sensorimotor cortices.

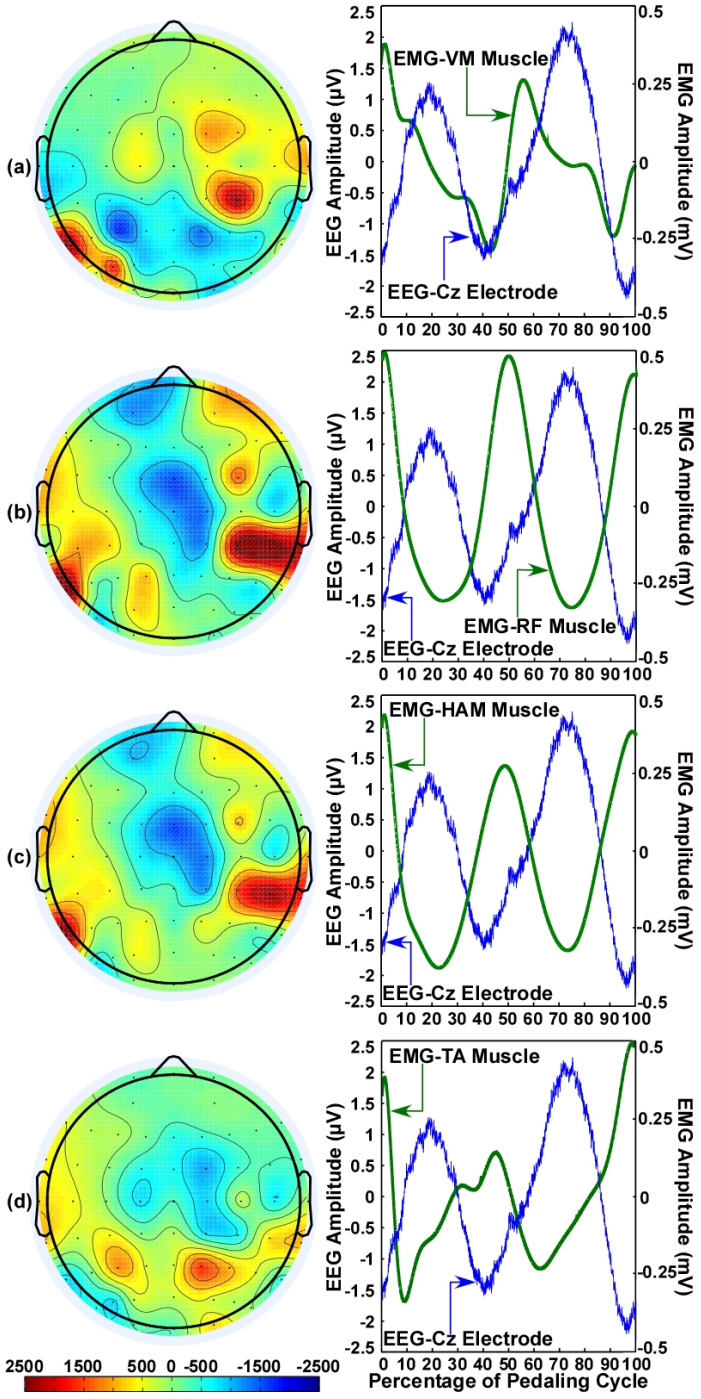

Figure 2.4 Correlation Results. 2-D topographic maps (Left Panel; [a-d]) showing the cross correlation coefficients (non-normalized) between the ensemble averaged EEG and the composite EMGs from the VM, RF, MH and TA muscles during active pedaling. The 2-D maps were created by interpolating the correlation coefficients obtained at each of the 64 electrodes over the scalp. The color map at the bottom shows range of the correlation coefficients. 2-D maps were generated using EEGLAB. The right panel shows the EEG waveform at the Cz electrode and the composite EMGs from the VM, RF, MH and TA muscles.

A significant negative cross-correlation between the group-averaged EEG waveform at the Cz electrode during active trials and the composite EMG waveforms (as explained above) were observed for the RF ($r = -0.77$, $p < 0.01$) the MH ($r = -0.85$, $p < 0.01$) and the TA ($r = -0.70$, $p < 0.01$) muscles (Figure 2.4). Also, the cross correlation coefficient (between the EEG and EMG waveforms) for these muscles was greatest for the electrodes overlying the approximate leg representation area of the sensorimotor cortex (Figure 2.4). Composite EMG waveforms for the VM and SOL muscles also had a significant correlation with the EEG waveform at the Cz electrode ($r = 0.25$, *and* 0.64 respectively, and $p < 0.01$ for both), but the correlation was not at maximum in the electrodes over the leg representation area of the sensorimotor cortex for either of these muscles.

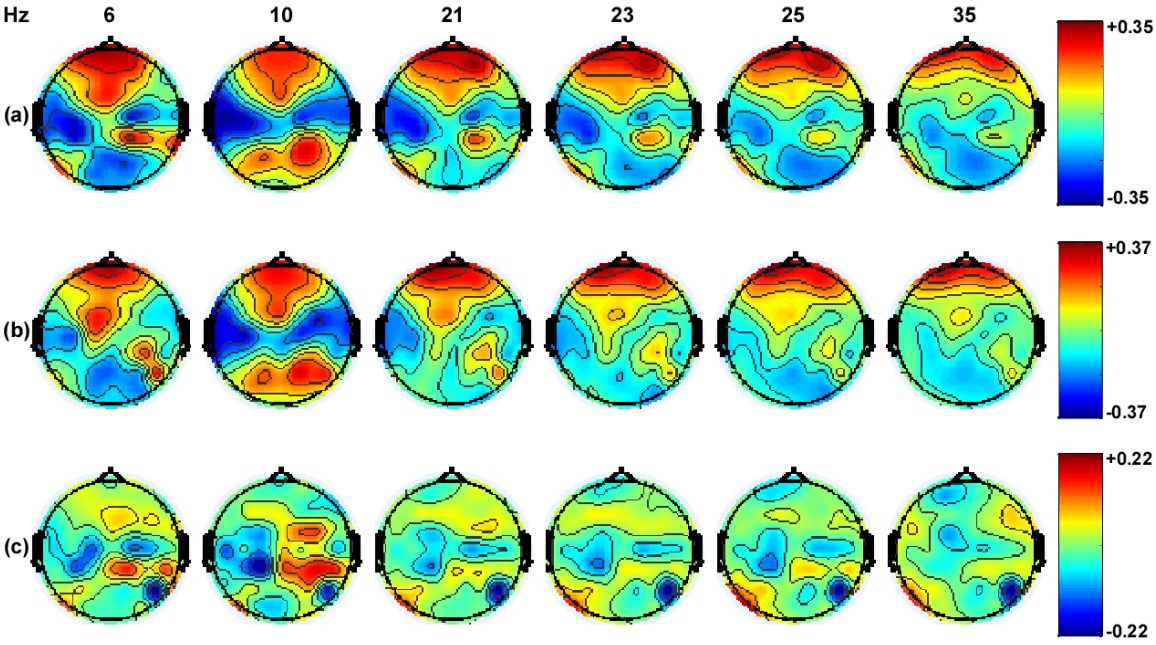

Figure 2.5 Frequency Domain Results. Group average topographic maps showing the amplitudes at selected frequencies within the α and β bands during active (a) and passive (b) pedaling. Maps in (c) were obtained by subtracting the passive from the active maps. The color map on the right shows the range for the amplitude of all 6 frequencies. These group average topographic maps were generated using EEGLAB.

Electrode	p-value	Electrode	p-value	Electrode	p-value
FC3	0.124	C3	0.80	CP3	0.109
FC1	0.203	**C1**	**0.034***	**CP1**	**0.005***
FCz	0.938	Cz	0.759	CPz	0.884
FC2	0.959	**C2**	**0.032***	CP2	0.169
FC4	0.659	C4	0.139	CP4	0.958

Table 2.2: (P-value table for central electrodes) P-values for paired t-test of the β power for active vs passive tasks for electrodes lying in the central rows of the cap. Significant differences (P<0.05) indicated by *.

Desynchrony (i.e. a decrease in amplitude of the power) of the center beta band (20-25 Hz) over the sensorimotor cortex was observed during both active and passive pedaling (Figure 2.5). A lower power at the beta band was spread diffusely over the scalp in both the active and the passive trials. However, group average subtraction maps (active task–passive task) revealed that lower power (20-25 Hz), consistent with desynchronization of the beta band frequencies, was significantly greater in the active as compared to the passive trials *(ANOVA; P(Task)<0.01; P(Electrode)=0.119; P(Task*Electrode)=0.101).* Also, paired t-test results (Table 2.2) revealed significantly lower β power in the C1, C2 and CP1 electrodes between the active and passive task *(P<0.05).* Note that the difference in the frequency amplitudes in active versus passive pedaling was better defined for frequencies near the middle of the β band (21, 23 and 25 Hz) than for the 10 and 35 Hz frequencies and were also localized near the sensorimotor cortices (Figure 2.5).

2.4 Discussion

Our results demonstrate the feasibility of using EEG to identify brain electrical activity during a locomotor task (pedaling). Electrical activity recorded using EEG was somatotopically located over the leg representation areas of the sensorimotor cortices and demonstrated a temporal pattern indicating an association with the phase of the pedaling cycle. The patterns of EEG signals recorded for the active and the passive trials showed similarity, suggesting predominance of cortical processing of sensory information generated by movement of the lower limbs. However, there were also indications that cortical activity also contributed to motor commands for pedaling. The EEG evidence for motor cortical activity contributions to active pedaling comprised the following: (i) attenuation of the EEG voltage during active pedaling, (ii) greater desynchrony in β band frequencies during active pedaling and (iii) correlation between EEG recorded from the Cz electrode and EMG from recorded from "transition muscles" during active pedaling.

2.4.1 EEG Ensemble-Averaged Waveform During Active and Passive Pedaling

The ensemble averaged waveform recorded at the Cz electrode during both active and passive pedaling were cyclical in nature, with approximately twice the frequency of the pedaling cycle. The cyclical nature of these slow cortical potentials and the alternating field potentials (Figure 2.3) suggests modulation of the brain activity during different phases of the pedaling cycle. These cortical potentials are similar to movement related brain potentials (MRBP), which are indicative of preparatory and execution stages of a voluntary action (Vaughan et al. 1968). MRBPs are characterized by a negative going waveform that indicates cortical activity during motor tasks (Shibasaki et al. 1980;

Barrett et al. 1986). The exact role of the peaks and valleys obtained during the oscillatory ensemble averaged waveform is unclear. The valleys might correspond to the motor potential required to drive the muscles, while the peaks might correspond to sensory processing. This hypothesis requires further investigation.

2.4.2 The Similarities in Active and Passive Conditions

As stated above, the similarity in the EEG waveform recorded at the Cz electrode during active and passive pedaling suggests that EEG signals during pedaling have a large component dedicated to the processing of afferent information from the lower limbs. Previous research quantifying brain activity during active and passive pedaling using PET has reported similar findings (Christensen et al. 2000). Specifically, there is increased activity in the bilateral primary motor, primary sensory and supplementary motor cortices, during active pedaling as compared to the rest condition. However, activation in identical areas with similar magnitude was also observed during passive pedaling (Christensen et al. 2000). In the current study, activity in the leg representation area of the primary motor cortex associated with active pedaling was apparent only after subtracting the passive activity patterns from the active trials. The magnitude of the ensemble-averaged voltages from the Cz electrode were also significantly different, with lower voltage fluctuations observed during the active condition.

One explanation for the similarity in the active and passive EEG waveforms is that the subjects might not have fully relaxed during the passive trials. However, EMG recorded during the passive trials did not show any activity suggesting active recruitment of the leg muscles. EMG was not recorded from the trunk muscles and arguably, there

could have been efferent corticospinal drive to these muscles for maintenance of trunk balance during passive pedaling. However, this is unlikely to have produced focused voltage changes over the leg representation area of the cortex as seen in the topographic maps.

The passive trials could have triggered imagined movements, which could have produced brain signals similar to those associated with active pedaling. The functional neuroanatomy associated with active and imagined movements have been previously documented to be similar in healthy subjects (Porro et al. 1996; Deiber et al. 1998; Stippich et al. 2002; Lacourse et al. 2005). In the current results, it appears unlikely that the activity observed during passive trials was due to imagined movements rather than afferent signals from the limbs. Our results indicated a localization of activity during passive trials that was posterior to the localization during active trials (insets in Figure 2.3). In contrast, motor imagery elicits activation in the prefrontal cortices and supplementary motor areas, which lie anterior to the motor cortex (Malouin et al. 2003). Thus it is unlikely, that the activity observed during the passive trials is due to the imagination of the movements.

2.4.3 The Differences in Active and Passive Conditions

Despite the apparent similarity between the EEG waveforms of the active and passive trials, there was a significant difference in the magnitude of the EEG signals generated in the two conditions. The amplitude (maximum positive - minimum negative deflection) of the EEG waveform at the Cz electrode was smaller in the active as compared to the passive trials. Topographic maps of the ensemble-averaged signals also

suggested the possibility of a slight anterior shift in the signals during the active compared to the passive condition (i.e. compare insets in Figure 2.3), consistent with an increase in primary motor cortical areas or a decrease in activity within the primary somatosensory cortex during the active task.

We postulate that the attenuation of the EEG waveform during active pedaling might have occurred due to centripetal gating of the sensory feedback by the efferent corticospinal output. Gating of sensory input during walking (Duysens et al. 1995; Altenmüller et al. 1995; Brooke et al. 1991a) and pedaling (Sakamoto et al. 2004; Brooke et al. 1992; Brooke et al. 1991b) had been previously described. When comparing the somatosensory evoked response to sural nerve stimulation during walking as compared to standing, a 38% decrease in the P50-N80 complex of the somatosensory evoked potential (SSEP) was observed during walking (Duysens et al. 1995). Further, Altenmuller et al. (1995) demonstrated that the early SSEP components (N40 and N40-P50 complex) were of similar magnitude during walking and standing, while the later SSEP components (P50-N80 and N80-P220) showed significant attenuation and splitting during walking. These findings have been interpreted as a gating of the sensory input by motor output at the level of the cortex. The spinal cord may also gate sensory feedback, as inhibition in transmission in propriospinal-like neurons at the level of spinal interneurons by corticospinal activity has also been observed during walking (Iglesias et al. 2008). Irrespective of the site of gating, afferent sensory input is inhibited by corticospinal drive; the decreased amplitude of the EEG signal during active pedaling may thus be a marker for corticospinal activity during pedaling.

2.4.4 Distribution of the Beta Band Frequency Amplitude During Active and Passive Pedaling

We did not see a focused area of decreased β band desynchronization over the leg representation of the sensorimotor cortex in either the active or the passive trials. Akin to the ensemble-averaged voltage waveforms, the frequency amplitude topography was similar in the active and the passive trials (Figure 2.5(a-b)). However, subtraction maps (β band topography during active trials - β band topography during passive trials) suggest that β desynchrony was significantly greater in regions around the leg representation area of the sensorimotor cortices in the active as compared to the passive trials (Figure 2.5c). These observations indicate a difference in brain activity during active pedaling, compared to passive movement of the limbs, and implicates the cortex in the control of pedaling movements.

Notice that the regions implicated in β band desynchronization were not exactly over the leg representation area of the motor cortex, but lateral to it (Figure 2.5). Christensen et al. have also described significant activation in a cortical area between the leg and the shoulder based on PET measurements during pedaling and postulated that this represented motor cortical activity driving the proximal leg muscles (Christensen et al. 2000). Since β desynchrony, in general, is a marker for voluntary motor activity, greater β desynchrony in the active trials may have been a marker for motor cortical activity during pedaling (Jasper et al. 1938; Chatrian et al. 1959; Jasper et al. 1949). Further, most of the motor cortical activity may have been directed towards recruiting proximal limb muscles.

While cortical motor activity is the most likely explanation for the increased β band desynchrony during active pedaling, a difference in the sensory signals produced by active pedaling may have contributed to the differences in β band desynchrony. β band desynchrony during times of active motor output is well recognized (Jasper et al. 1938; Chatrian et al. 1959; Chatrian et al. 1959; Jasper et al. 1949); however, there is also an effect of somatosensory feedback on brain oscillations. Brief somatosensory stimuli are followed by increased desynchronization in the 20 Hz (and 10 Hz) oscillations over the bilateral primary sensorimotor cortices, followed by a rebound post-stimulus synchronization in the 20 Hz oscillations in the contralateral primary sensorimotor cortex and in the supplementary motor area (Pfurtscheller 1981; Jasper et al. 1938; Kuhlman 1978; Salmelin et al. 1994; Salenius et al. 1997). If the effect of a continuous somatosensory input (as occurs in pedaling) on brain oscillations is similar to that of somatosensory stimulation, increased β band desynchrony may well have been the result of an increased sensory input due to voluntary muscle contractions during active pedaling. β band desynchrony that is caused by sensory afferents would also explain the similarities of β band topography between the active and the passive trials.

2.4.5 Correlation Between EEG Activity and EMG From Leg Muscles

EEG activity recorded at the Cz electrode had a strong negative correlation with the composite (bilateral) EMGs of the RF, MH and TA muscles, transition muscles of pedaling (Raasch et al. 1999; Neptune et al. 1997). Specifically, the association between EEG and EMG of these three transition muscles suggests involvement of the motor cortex during the relatively challenging task of transitioning between the flexion and

extension phases of cycling. There is some evidence that muscles contributing to limb transitions during pedaling may have unique cortical control. For example, in stroke subjects, unilateral pedaling with either the paretic or the non-paretic leg strongly activates the muscles contributing to limb transition (e.g. RF and MH) in the stationary leg, while the muscles comprising the plantar-dorsiflexor functions are only weakly activated under similar conditions (Kautz et al. 2006; Kautz et al. 2002b). While the effect occurs in both legs, it is more pronounced when subjects pedal with the paretic leg and in subjects with a more severe stroke (Kautz et al. 2006). These observations suggest that corticospinal output that normally inhibits the excitatory intralimb pathways and prevents muscle activity in the stationary leg is lost after stroke (Kautz et al. 2006; Kautz et al. 2005b). Since the greatest effect is seen in the activity of the transition muscles, it can be presumed that the corticospinal control is more crucial to the activity of these muscles during a locomotor like task.

2.4.6 Does the Cortex Participate in the Control of Locomotor Function in Humans?

There is evidence to suggest that processing of sensory information from the muscles and skin of lower limbs during locomotion occurs at a cortical level and that cortical motor activity is involved in walking. For example, based on the characteristics of the dorsiflexor stretch reflex responses during walking, the brain pathways appear to modulate stretch reflexes during walking (Christensen et al. 2001; Petersen et al. 1998). Similarly, transcranial magnetic stimulation modulates H-reflexes during walking in a phase-dependent manner, supporting the concept of cortical regulation of spinal reflexes

during gait (Christensen et al. 2001; Petersen et al. 1998). Similarly, it has been shown that the cutaneous reflex response has a transcortical component that is modulated by the phase of gait (Christensen et al. 1999; Nielsen et al. 2002). Our observations of EEG activity that modulates during pedaling, with significant differences during active and passive pedaling, are consistent with a role for the sensorimotor cortices in the regulation of gait.

While cortical involvement in the motor control of pedaling might have corollaries to cortical control of walking, there remain differences in control of the two tasks. Unlike gait, pedaling is constrained to a circular trajectory, there is minimal need for trunk balance (especially with the semi reclining backboard, as used in this study) and there is no requirement of balancing on a single leg during any phase of pedaling. However, broad similarities in the biomechanics of pedaling and walking and between brain activation during pedaling (Christensen et al. 2000) and immediately after walking (Fukuyama et al. 1997) has been previously described. Therefore despite the obvious dissimilarities between pedaling and walking, pedaling might serve as a reduced model to study the cortical control of locomotion and it's impairment after a neurological injury (Schindler-Ivens et al. 2008; Kautz et al. 2006; Kautz et al. 2005a; Kautz et al. 2002a; Schindler-Ivens et al. 2004). As demonstrated in this study, EEG can be used to record brain activity during pedaling and may therefore provide valuable information if applied to these situations.

2.5 Conclusion

In summary, this study demonstrates EEG signals during pedaling that suggest a role of cortical activity in pedaling. However, evidence for motor cortical activity during pedaling could only be indirectly ascertained, since a substantial amount of brain activity during pedaling appeared to be associated with the processing the sensory information. Correlation of the EMG recorded from the transition muscles and the EEG during pedaling suggested corticospinal control over the activity of these muscles during locomotion. Thus, transitions from flexion to extension (and *vice versa*) during walking may be the locomotor function most vulnerable to impairment after an injury to the cortex, as in stroke.

3 FUTURE DIRECTIONS

The aim of this study was to demonstrate the role of the sensorimotor cortex in locomotor-type activity. This study has successfully established EEG as an imaging modality for performing locomotion-related studies. The long-term goals for this project are to develop rehabilitative techniques to assist patients with stroke or spinal cord injury. However, to achieve this goal a better understanding of the role of supraspinal networks during locomotion in normal subjects is required. Although the roles of the CPG and peripheral networks are equally important, we will focus on supraspinal networks. Here we discuss a few short-term strategies we can implement to improve our study in the future:

3.1 Initiation and Termination of Locomotion

Problem: The neural structure(s) involved in initiating and terminating movement in humans is unclear.

Solution: Animal studies have identified a role of the reticulospinal system in producing the descending drive to initiate locomotion. Similarly, we would expect movement initiation and termination to be controlled through supraspinal drive. To investigate this problem, a basic pedaling experimental setup similar to ours could be used with some modifications. Firstly, a block design format similar to what is used in fMRI could be implemented. This would allow us to capture movement initiation and termination within each pedaling block (which cannot be easily achieved during continuous pedaling). Secondly, the pedaling cycle would need to be uniform in length (e.g. by timing it to a metronome) while performing the task. This would allow us to

compare observations during the initial and end segments of every movement cycle across trials. Analyzing these segments would help reveal the neural structures involved in the initiation and termination of locomotion.

3.2 Mechanism to Modulate Speed and Power Exerted During Locomotion

Problem: The mechanism and specific supraspinal structures that modulate speed and power during locomotion are unknown.

Solution: Speed and power exerted during locomotion are important parameters to quantify locomotion. To study this, we could accelerate and decelerate the crank in the pedaling experiment to record changes in neural activity associated with changes in speed. Similarly, resistance during pedaling can be increased and decreased to record neural activity associated with changes in power exertion. Analyzing this data may reveal mechanisms and neural structures with different activation levels for different levels of speed and power, thus indicating their role in controlling these parameters.

3.3 Understanding Relative Timings of Cortical Structures During Locomotion

Problem: Poor source localization results due to low signal to noise ratio and low spatial resolution of EEG.

Solution: Different methods such as independent component analysis (ICA) and dipole source localization can be used to identify different cortical and sub-cortical structures involved during different phases of the gait cycle. It is possible that the data recorded using EEG may have insufficient signal to noise ratio (SNR) thereby preventing reliable source localization. In such cases, the pedaling task can be performed within a

magnetoencephalography (MEG) scanner. The MEG is advantageous over fMRI in that it has better temporal resolution with good spatial resolution. Also, there are algorithms already built to compute source (dipole) localization and ICA using MEG data. Thus, MEG can provide a better understanding of the relative timings of the various cortical and sub-cortical structures during various phases of the gait cycle.

Furthermore, MEG would be a reasonable imaging modality in locomotion studies to help uncover the neural correlates of movement initiation and termination and the neural structures involved in modulating the speed and power of movement.

3.4 Neural Correlates of Fine Control of Limb Trajectory and Foot Placement

Problem: The neural correlates modulating the fine control of limb trajectory and foot placement are unclear.

Solution: Investigating the fine control of locomotion is not possible inside a scanner using a pedaling paradigm. An alternative experimental method could be to use treadmill walking while applying somatosensory evoked potentials (SSEP's) to understand cortical activity during gait. A previous study by Duysens et al. (1995) has shown the modulation of sensation according to the phase of the gait cycle. For example, the SSEP's recorded are significantly decreased at the start of the stance phase compared to the end of the swing phase. Thus, SSEP's during walking can be used to probe the role of the cortex during fine control of locomotion in humans.

To conclude, the basic question remains to identify the mechanism by which the supraspinal networks use sensory information to generate motor commands which in turn modify the CPG to control the peripheral muscles. Answering the questions mentioned

above would assist the development of rehabilitative techniques for improving gait in subjects with stroke or spinal cord injury.

BIBLIOGRAPHY

Altenmüller E, Berger W, Prokop T, Trippel M and Dietz V. Modulation of sural nerve somatosensory evoked potentials during stance and different phases of the step-cycle. *Electroencephalogr Clin Neurophysiol* 96: 6: 516-525, 1995.

American Clinical Neurophysiology Society. Guideline 5: Guidelines for standard electrode position nomenclature. *J Clin Neurophysiol* 23: 2: 107-110, 2006.

Amos A, Armstrong D and Marple-Horvat D. Responses of motor cortical neurones in the cat to unexpected perturbations of locomotion. *Neurosci Lett* 104: 1-2: 147-151, 1989.

Amos A, Armstrong D and Marple-Horvat D. A ladder paradigm for studying skilled and adaptive locomotion in the cat. *J Neurosci Methods* 20: 4: 323-340, 1987.

Andersson O and Grillner S. Peripheral control of the cat's step cycle: II. Entrainment of the central pattern generators for locomotion by sinusoidal hip movements during fictive locomotion. *Acta Physiol Scand* 118: 229-239, 1983.

Andersson O and Grillner S. Peripheral control of the cat's step cycle: I. Phase dependent effects of ramp-movements of the hip during 'fictive locomotion'. *Acta Physiol Scand* 113: 89-102, 1981.

Armstrong D and Edgley S. Discharges of Purkinje cells in the paravermal part of the cerebellar anterior lobe during locomotion in the cat. *J Physiol (Lond)* 352: 403-424, 1984b.

Armstrong D and Edgley S. Discharges of nucleus interpositus neurones during locomotion in the cat. *J Physiol (Lond)* 351: 411-432, 1984a.

Armstrong D and Marple-Horvat D. Role of the cerebellum and motor cortex in the regulation of visually controlled locomotion. *Can J Physiol Pharmacol* 74: 4: 443-455, 1996.

Babu R and Namasivayam A. Recovery of bipedal locomotion in bonnet macaques after spinal cord injury: footprint analysis. *Synapse* 62: 6: 432-447, 2008.

Bakker M, De Lange F, Helmich R, Scheeringa R, Bloem B and Toni I. Cerebral correlates of motor imagery of normal and precision gait. *Neuroimage* 41: 3: 998-1010, 2008.

Barbeau H and Fung J. The role of rehabilitation in the recovery of walking in the neurological population. *Curr Opin Neurol* 14: 6: 735-740, 2001.

Barrett G, Shibasaki H and Neshige R. Cortical potentials preceding voluntary movement: evidence for three periods of preparation in man. *Electroencephalogr Clin Neurophysiol* 63: 4: 327-39, 1986.

Beloozerova I and Sirota M. The role of the motor cortex in the control of accuracy of locomotor movements in the cat. *J Physiol (Lond)* 461: 1-25, 1993.

Bolton D, Tse A, Ballermann M, Misiaszek J and Fouad K. Task specific adaptations in rat locomotion: runway versus horizontal ladder. *Behav Brain Res* 168: 2: 272-279, 2006.

Brooke J, Colledge M, Collins D and Mcllroy W. Long latency responses evoked in leg muscles during sitting and pedalling. *Can J Physiol Pharmacol* 69: 1991b.

Brooke J, Collins D, Boucher S and McIlroy W. Modulation of human short latency reflexes between standing and walking. *Brain Res* 548: 1-2: 172-8, 1991a.

Brooke J, McIlroy W and Collins D. Movement features and H-reflex modulation. I. Pedalling versus matched controls. *Brain Res* 582: 1: 78-84, 1992.

Brown TG. The intrinsic factors in the act of progression in the mammal. 84: 308-319, 1911.

Brown D and Kautz S. Increased workload enhances force output during pedaling exercise in persons with poststroke hemiplegia. *Stroke* 29: 3: 598-606, 1998.

Brown D, Kautz S and Dairaghi C. Muscle activity adapts to anti-gravity posture during pedalling in persons with post-stroke hemiplegia. *Brain* 120: Pt 5: 825-837, 1997.

Brown D and Kukulka C. Human flexor reflex modulation during cycling. *J Neurophysiol* 69: 1212-1224, 1993.

Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A and Held J. Myoclonus in a patient with a spinal cord transection. *Brain* 111: 1235-45, 1988.

Bussel B, Roby-Brami A, Remi Neris O and Yakovleff A. Evidence for a spinal stepping generator in man. *Paraplegia* 34: 91-2, 1996.

Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G and Green B. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. *Brain* 117 (Pt 5): 1143-1159, 1994.

Capaday C, Lavoie B, Barbeau H, Schneider C and Bonnard M. Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J Neurophysiol* 81: 1: 129-139, 1999.

Cerminara N, Edge A, Marple-Horvat D and Apps R. The lateral cerebellum and visuomotor control. *Prog Brain Res* 148: 213-226, 2005.

Chatrian G, Petersen M and Lazarte J. The blocking of the rolandic wicket rhythm and some central changes related to movement. *Electroenceph clin Neurophysiol* 11: 497-510, 1959.

Christensen L, Andersen J, Sinkjaer T and Nielsen J. Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *J Physiol* 531: Pt 2: 545-557, 2001.

Christensen L, Johannsen P, Sinkjaer T, Petersen N, Pyndt H and Nielsen J. Cerebral activation during bicycle movements in man. *Exp Brain Res* 135: 1: 66-72, 2000.

Christensen L, Morita H, Petersen N and Nielsen J. Evidence suggesting that a transcortical reflex pathway contributes to cutaneous reflexes in the tibialis anterior muscle during walking in man. *Exp Brain Res* 124: 1: 59-68, 1999.

Ciccarelli O, Toosy A, Marsden J, Wheeler-Kingshott C, Sahyoun C, Matthews P, Miller D and Thompson A. Identifying brain regions for integrative sensorimotor processing with ankle movements. *Exp Brain Res* 166: 1: 31-42, 2005.

Coast J and Welch H. Linear increase in optimal pedal rate with increased power output in cycle ergometry. *Eur J Appl Physiol Occup Physiol* 53: 4: 339-342, 1985.

Conway B, Hultborn H and Kiehn O. Proprioceptive input resets central locomotor rhythm in the spinal cat. *Exp Brain Res* 68: 643-656, 1987.

Courtine G, Roy R, Raven J, Hodgson J, McKay H, Yang H, Zhong H, Tuszynski M and Edgerton V. Performance of locomotion and foot grasping following a unilateral thoracic corticospinal tract lesion in monkeys (Macaca mulatta). *Brain* 128: Pt 10: 2338-2358, 2005.

Deiber M, Ibañez V, Honda M, Sadato N, Raman R and Hallett M. Cerebral processes related to visuomotor imagery and generation of simple finger movements studied with positron emission tomography. *Neuroimage* 7: 2: 73-85, 1998.

Delorme A and Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 134: 1: 9-21, 2004.

Deutschlander A, Stephan T, Hufner K, Wagner J, Wiesmann M, Strupp M, Brandt T and Jahn K. Imagined locomotion in the blind: an fMRI study. *Neuroimage* 45: 1: 122-128, 2009.

Dietz V, Muller R and Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. *Brain* 125: 2626-2634, 2002.

Dimitrijevic M, Gerasimenko Y and Pinter M. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* 860: 360-376, 1998.

Dobkin B, Barbeau H, Deforge D, Ditunno J, Elashoff R, Apple D, Basso M, Behrman A, Harkema S, Saulino M, Scott M and Spinal Cord Injury Locomotor Trial Group. The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. *Neurorehabil Neural Repair* 21: 1: 25-35, 2007.

Dobkin B, Firestine A, West M, Saremi K and Woods R. Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation. *Neuroimage* 23: 1: 370-381, 2004.

Dobkin B, Harkema S, Requejo P and Edgerton V. Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. *J Neurol Rehabil* 9: 4: 183-90, 1995.

Donelan J and Pearson K. Contribution of sensory feedback to ongoing ankle extensor activity during the stance phase of walking. *Can J Physiol Pharmacol* 82: 8-9: 589-598, 2004.

Dow R and Moruzzi G. *The physiology and pathology of the cerebellum.* Minneapolis: University of Minnesota Press, 1958.

Drew T, Jiang W and Widajewicz W. Contributions of the motor cortex to the control of the hindlimbs during locomotion in the cat. *Brain Res Brain Res Rev* 40: 1-3: 178-191, 2002.

Duysens J, Clarac F and Cruse H. Load-regulating mechanisms in gait and posture: comparative aspects. *Physiol Rev* 80: 1: 83-133, 2000.

Duysens J and Pearson K. Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Res* 187: 2: 321-332, 1980.

Duysens J, Tax A, Nawijn S, Berger W, Prokop T and Altenmüller E. Gating of sensation and evoked potentials following foot stimulation during human gait. *Exp Brain Res* 105: 3: 423-431, 1995.

Eidelberg E, Walden J and Nguyen L. Locomotor control in macaque monkeys. *Brain* 104: 647-663, 1981.

Ericson M. Mechanical muscular power output and work during ergometer cycling at different work loads and speeds. *Eur J Appl Physiol Occup Physiol* 57: 4: 382-387, 1988.

Faist M, Hoefera C, Hodappa M, Dietzb V, Bergera W and Duysens J. In humans Ib facilitation depends on locomotion while suppression of Ib inhibition requires loading. *Brain research* 1076: 87-92, 2006.

Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J and Shibasaki H. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett* 228: 3: 183-186, 1997.

Gordon K, Wu M, Kahn J, Dhaher Y and Schmit B. Ankle Load Modulates Hip Kinetics and EMG During Human Locomotion. *J Neurophysiol* 101: 2062-2076, 2009.

Grillner S and Rossignol S. On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Res* 146: 2: 269-277, 1978.

Harkema S, Hurley S, Patel U, Requejo P, Dobkin B and Edgerton V. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol* 77: 797-811, 1997.

Iglesias C, Nielsen J and Marchand-Pauvert V. Corticospinal inhibition of transmission in propriospinal-like neurones during human walking. *Eur J Neurosci* 28: 7: 1351-1361, 2008.

Iseki K, Hanakawa T, Shinozaki J, Nankaku M and Fukuyama H. Neural mechanisms involved in mental imagery and observation of gait. *Neuroimage* 41: 3: 1021-1031, 2008.

Jacobs R and Macpherson J. Two functional muscle groupings during postural equilibriumin standing cats. 76: 2402-2411, 1996.

Jahanshahi M, Jenkins I, Brown R, Marsden C, Passingham R and Brooks D. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain* 118 (Pt 4): 913-933, 1995.

Jahn K, Deutschländer A, Stephan T, Kalla R, Wiesmann M, Strupp M and Brandt T. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *Neuroimage* 39: 2: 786-792, 2008.

Jasper H and Andrews H. Electro-encephalography III. Normal differentiation of occipital and precentral regions in man. *Arch Neurol Psychiatry* 39: 96-115, 1938.

Jasper H and Penfield W. Electrocorticograms in man: effect of the voluntary movement upon the electrical activity of the precentral gyrus. *Arch Psychiatry Z Neurol* 183: 163-174, 1949.

Kably B and Drew T. Corticoreticular pathways in the cat. II. Discharge activity of neurons in area 4 during voluntary gait modifications. *J Neurophysiol* 80: 1: 406-424, 1998.

Kautz S and Brown D. Relationships between timing of muscle excitation and impaired motor performance during cyclical lower extremity movement in post-stroke hemiplegia. *Brain* 121: Pt 3: 515-26, 1998.

Kautz S, Brown D, Van der Loos H and Zajac F. Mutability of bifunctional thigh muscle activity in pedaling due to contralateral leg force generation. *J Neurophysiol* 88: 3: 1308-1317, 2002a.

Kautz S, Brown D, Van der Loos H and Zajac F. Mutability of bifunctional thigh muscle activity in pedaling due to contralateral leg force generation. *J Neurophysiol* 88: 3: 1308-17, 2002b.

Kautz S and Patten C. Interlimb influences on paretic leg function in poststroke hemiparesis. *J Neurophysiol* 93: 5: 2460-2473, 2005a.

Kautz S and Patten C. Interlimb influences on paretic leg function in poststroke hemiparesis. *J Neurophysiol* 93: 5: 2460-73, 2005b.

Kautz S, Patten C and Neptune R. Does unilateral pedaling activate a rhythmic locomotor pattern in the nonpedaling leg in post-stroke hemiparesis? *J Neurophysiol* 95: 5: 3154-3163, 2006.

Kelly-Hayes M, Beiser A, Kase C, Scaramucci A, D'Agostino R and Wolf P. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis* 12: 3: 119-126, 2003.

Kriellaars D, Brownstone R, Noga B and Jordan L. Mechanical entrainment of fictive locomotion in the decerebrate cat. *J Neurophysiol* 71: 2074-2086, 1994.

Kuhlman W. Functional topography of the human mu rhythm. *Electroencephalogr Clin Neurophysiol* 44: 1: 83-93, 1978.

Lacourse M, Orr E, Cramer S and Cohen M. Brain activation during execution and motor imagery of novel and skilled sequential hand movements. *Neuroimage* 27: 3: 505-19, 2005.

Lacquaniti F, Maioli C and Fava E. Cat posture on the tilted platform. 57: 82: 88, 1984.

Lajoie K and Drew T. Lesions of area 5 of the posterior parietal cortex in the cat produce errors in the accuracy of paw placement during visually guided locomotion . *J Neurophysiol* 97: 3: 2339-2354, 2007a.

Lajoie K and Drew T. A novel locomotor task to study the control of visually-guided locomotion in the cat: behavioural strategies and the effects of unilateral lesion of the posterior parietal cortex. *J Neurophysiol* 97: 2339-2354, 2007b.

Lam T and Pearson K. Proprioceptive modulation of hip flexor activity during the swing phase of locomotion in decerebrate cats. *J Neurophysiol* 86: 3: 1321-1332, 2001.

Lehmann D and Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr Clin Neurophysiol* 48: 6: 609-621, 1980.

Little J, Harris R and Sohlberg R. Locomotor recovery following subtotal spinal cord lesions in a rat model. *Neurosci Lett* 87: 1-2: 189-194, 1988.

Lopes da Silva F. Neural mechanisms underlying brain waves: from neural membranes to networks. *Electroencephalogr Clin Neurophysiol* 79: 2: 81-93, 1991.

Lünenburger L, Bolliger M, Czell D, Müller R and Dietz V. Modulation of locomotor activity in complete spinal cord injury. *Exp Brain Res* 174: 4: 638-46, 2006.

Lyalka V, Zelenin P, Karayannidou A, Orlovsky G, Grillner S and Deliagina T. Impairment and recovery of postural control in rabbits with spinal cord lesions. *J Neurophysiol* 94: 6: 3677-3690, 2005.

Malouin F, Richards C, Jackson P, Dumas F and Doyon J. Brain activations during motor imagery of locomotor-related tasks: a PET study. *Hum Brain Mapp* 19: 1: 47-62, 2003.

Marple-Horvat D, Criado J and Armstrong D. Neuronal activity in the lateral cerebellum of the cat related to visual stimuli at rest, visually guided step modification, and saccadic eye movements. *J Physiol (Lond)* 506 (Pt 2): 489-514, 1998.

Matsuyama K and Drew T. Vestibulospinal and reticulospinal neuronal activity during locomotion in the intact cat. II. Walking on an inclined plane. *J Neurophysiol* 84: 5: 2257-2276, 2000.

McCrea D. Spinal circuitry of sensorimotor control of locomotion. *J Physiol (Lond)* 533: 41-50, 2001.

McVea D, Donelan J, Tachibana A and Pearson K. A role for hip position in initiating the swing-to-stance transition in walking cats. *J Neurophysiol* 94: 5: 3497-3508, 2005.

McVea D and Pearson K. Long-lasting, context-dependent modification of stepping in the cat after repeated stumbling-corrective responses. *J Neurophysiol* 97: 1: 659-669, 2007.

Mehta J, Verber M, Wieser J, Schmit B and Schindler-Ivens S. A novel technique for examining human brain activity associated with pedaling using fMRI. *J Neurosci Methods* 179: 2: 230-239, 2009.

Misulis K and Head T. *Essentials of Clinical Neurophysiology.* Butterworth-Heinemann Press, 2003.

Miyai I, Tanabe H, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T and Kubota K. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* 14: 5: 1186-1192, 2001.

Nathan P. Effects on movement of surgical incisions into the human spinal cord. *Brain* 117 (Pt 2): 337-346, 1994.

Neptune R, Kautz S and Hull M. The effect of pedaling rate on coordination in cycling. *J Biomech* 30: 10: 1051-1058, 1997.

Neuper C and Pfurtscheller G. Post-movement synchronization of beta rhythms in the EEG over the cortical foot area in man. *Neurosci Lett* 216: 17–20, 1996.

Neuroscan C. *Edit 4.3 User's Manual*. 2003.

Nielsen J. How we walk: central control of muscle activity during human walking. *Neuroscientist* 9: 3: 195-204, 2003.

Nielsen J and Sinkjaer T. Afferent feedback in the control of human gait. *J Electromyogr Kinesiol* 12: 3: 213-217, 2002.

Orlovsky G. Work of the Purkinje cells during locomotion. *Biophysics* 17: 935â€“941, 1972.

Pang M and Yang J. The initiation of the swing phase in human infant stepping: importance of hip position and leg loading. *J Physiol (Lond)* 528 Pt 2: 389-404, 2000.

Pearson K. Proprioceptive regulation of locomotion. *Curr Opinion Neurobiol* 5: 786-791, 1995.

Pearson K. Common principles of motor control in vertebrates and invertebrates. *Annu Rev Neurosci* 16: 265-297, 1993.

Pearson K, Ramirez J and Jiang W. Entrainment of the locomotor rhythm by group Ib afferents from ankle extensor muscles in spinal cats. *Exp Brain Res* 90: 3: 557-566, 1992.

Petersen N, Christensen L, Morita H, Sinkjaer T and Nielsen J. Evidence that a transcortical pathway contributes to stretch reflexes in the tibialis anterior muscle in man. *J Physiol (Lond)* 512 (Pt 1): 267-276, 1998.

Petersen N, Butler J, Marchand-Pauvert V, Fisher R, Ledebt A, Pyndt H, Hansen N and Nielsen J. Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *J Physiol (Lond)* 537: 651-656, 2001.

Pfurtscheller G. Central beta rhythm during sensory motor activities in man. *Electroenceph clin Neurophysiol* 51: 253-264, 1981.

Pfurtscheller G. Event-related synchronization (ERS): an electrophysiological correlate of cortical areas at rest. *Electroenceph clin Neurophysiol* 83: 62-69, 1992.

Porro C, Francescato M, Cettolo V, Diamond M, Baraldi P, Zuiani C, Bazzocchi M and di Prampero P. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. *J Neurosci* 16: 23: 7688-98, 1996.

Porter R and Lemon R. *Corticospinal function and voluntary movement.* New York: Oxford University Press, 1993.

Raasch C and Zajac F. Locomotor strategy for pedaling: muscle groups and biomechanical functions. *J Neurophysiol* 82: 2: 515-525, 1999.

Raasch C, Zajac F, Ma B and Levine WS. Muscle coordination of maximum-speed pedaling. *J Biomech* 30: 6: 595-602, 1997.

Rosenfeld J, Sherwood A, Halter J and Dimitrijevic M. Evidence of a pattern generator in paralyzed subject with spinal cord stimulation. *Soc Neurosci Abstr* 21: 688, 1995.

Rossignol S. Locomotion and its recovery after spinal injury. *Curr Opin Neurobiol* 10: 6: 708-716, 2000.

Rossignol S, Bouyer L, Langlet C, Barthelemy D, Chau C, Giroux N, Brustein E, Marcoux J, Leblond H and Reader T. Determinants of locomotor recovery after spinal injury in the cat. *Prog Brain Res* 143: 163-172, 2004.

Rossignol S, Dubuc R and Gossard J. Dynamic sensorimotor interactions in locomotion. *Physiol Rev* 86: 1: 89-154, 2006.

Sahyoun C, Floyer-Lea A, Johansen-Berg H and Matthews P. Towards an understanding of gait control: brain activation during the anticipation, preparation and execution of foot movements. *Neuroimage* 21: 2: 568-575, 2004.

Sakamoto M, Nakajima T, Wasaka T, Kida T, Nakata H, Endoh T, Nishihira Y and Komiyama T. Load- and cadence-dependent modulation of somatosensory evoked potentials and Soleus H-reflexes during active leg pedaling in humans. *Brain Res* 1029: 2: 272-285, 2004.

Salenius S, Schnitzler A, Salmelin R, Jousmäki V and Hari R. Modulation of human cortical rolandic rhythms during natural sensorimotor tasks. *Neuroimage* 5: 3: 221-8, 1997.

Salmelin R and Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience* 60: 2: 537-550, 1994.

Schindler-Ivens S, Brown D and Brooke J. Direction-dependent phasing of locomotor muscle activity is altered post-stroke. *J Neurophysiol* 92: 4: 2207-2216, 2004.

Schindler-Ivens S, Brown D, Lewis G, Nielsen J, Ondishko K and Wieser J. Soleus H-reflex excitability during pedaling post-stroke. *Exp Brain Res* 188: 3: 465-474, 2008.

Schmitt D. Insights into the evolution of human bipedalism from experimental studies of humans and other primates. *J Exp Biol* 206: Pt 9: 1437-1448, 2003.

Schubert M, Curt A, Jensen L and Dietz V. Corticospinal input in human gait: modulation of magnetically evoked motor responses. *Exp Brain Res* 115: 2: 234-246, 1997.

Shapkova E and Schomburg E. Two types of motor modulation underlying human stepping evoked by spinal cord electrical stimulation (SCES). *Acta Physiol Pharmacol Bulg* 26: 155-157, 2001.

Sherrington C. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol (Lond)* 40: 1-2: 28-121, 1910.

Shibasaki H, Barrett G, Halliday E and Halliday A. Components of the movement-related cortical potential and their scalp topography. *Electroencephalogr Clin Neurophysiol* 49: 3-4: 213-26, 1980.

Sinkjaer T, Andersen J, Ladouceur M, Christensen L and Nielsen J. Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *J Physiol (Lond)* 523 Pt 3: 817-827, 2000.

Sockol M, Raichlen D and Pontzer H. Chimpanzee locomotor energetics and the origin of human bipedalism. *Proc Natl Acad Sci U S A* 104: 30: 12265-12269, 2007.

Stecina K, Quevedo J and McCrea D. Parallel reflex pathways from flexor muscle afferents evoking resetting and flexion enhancement during fictive locomotion and scratch in the cat. *J Physiol (Lond)* 569: 275-290, 2005.

Stein J and Glickstein M. Role of the cerebellum in visual guidance of movement. *Physiol Rev* 72: 4: 967-1017, 1992.

Stephens M and Yang J. Short latency, non-reciprocal group I inhibition is reduced during the stance phase of walking in humans. *Brain Res* 743: 24-31, 1996.

Stippich C, Ochmann H and Sartor K. Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett* 331: 1: 50-4, 2002.

Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T and Kubota K. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. *NeuroImage* 23: 3: 1020-1026, 2004.

Toga A and Mazziotta J. *Brain Mapping: The Methods.* Academic Press, 2002.

Vaughan HJ, Costa L and Ritter W. Topography of the human motor potential. *Electroencephalogr Clin Neurophysiol* 25: 1: 1-10, 1968.

Wagner J, Stephan T, Kalla R, Bruckmann H, Strupp M, Brandt T and Jahn K. Mind the bend: cerebral activations associated with mental imagery of walking along a curved path. *Exp Brain Res* 191: 2: 247-255, 2008.

Wernig A, Müller S, Nanassy A and Cagol E. Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. *Eur J Neurosci* 7: 4: 823-829, 1995.

Whelan P. Control of locomotion in the decerebrate cat. *Prog Neurobiol* 49: 481-515, 1996.

Whelan P, Hiebert G and Pearson K. Stimulation of the group I extensor afferents prolongs the stance phase in walking cats. *Exp Brain Res* 103: 1: 20-30, 1995.

Whelan P and Pearson K. Comparison of the effects of stimulating extensor group I afferents on cycle period during walking in conscious and decerebrate cats. *Exp Brain Res* 117: 3: 444-452, 1997.

Winter D. Biomechanical motor patterns in normal walking. *J Mot Behav* 15: 302-330, 1983.

Wu M and Schmit B. Spastic reflexes trigerred by ankle load release in human spinal cord injury. *J Neurophysiol* 96: 2941-2950, 2006.

Yang J, Stephens M and Vishram R. Infant Stepping: a method to study the sensory control of human walking. *J Physiol* 507: 927-937, 1998a.

Yu J and Eidelberg E. Recovery of locomotor function in cats after localized cerebellar lesions. *Brain Res* 273: 1: 121-131, 1983.

APPENDIX 1

2-D Topography Mapping Algorithm

The 2-D topographic maps generated for the time-domain results were generated using SCAN 4.3 (Compumedics Neuroscan, El Paso TX). Scan 4.3 generates 2-D topographic maps using either of the two interpolation algorithms:

1) Local interpolation method
2) Global interpolation method

The local interpolation algorithm uses EEG potentials recorded at 1-4 nearest electrodes to calculate values at any given time point. The global interpolation algorithm uses EEG potentials recorded from all 64 electrodes to calculate values at any given time point. These values are then used to plot 2-D topographic maps at a particular time point. Detailed explanation for global interpolation method (Neuroscan, 2003) is discussed ahead. This particular approach provides with smoother maps compared to other algorithms like local interpolation algorithm. The time domain results presented previously are generated using this global interpolation algorithm.

The Global interpolation function $g(x, y)$ can be computed as follows

$$\mathbf{g}(x, y) = \mathbf{w}(x, y)^t \, \mathbf{W}^{-1} v \qquad [1]$$

Here, $g(x, y)$ is the globally interpolated value at map coordinates x and y and at a given time instance; $\mathbf{w}(x, y)^t$ is a column vector of 64 elements of inverse distance squared weights of the map coordinates with respect to electrode locations (Equation 2). The "t" superscript implies transpose operation on vector **w. W** is a 64 X 64 symmetric

matrix of inter-electrode inverse distance squared weights (Equation 3). *v* is a row vector of 64 columns representing the EEG potential measurements across all channels.

Every element of the weight vectors $\mathbf{w}(x, y)$ is computed using the formula

$$w_i(x, y) = ((x - x_i)^2 + (y - y_i)^2 + a)^{-1} \quad [2]$$

where x_i and y_i are coordinates of the i^{th} electrode and a is the average inter-electrode distance.

Every element of the symmetric matrix **W** is computed using the formula

$$W_{ij} = ((x_i - x_j)^2 + (y_i - y_j)^2 + a)^{-1} \quad [3]$$

where *i* and *j* are indices for electrodes and a is the average inter-electrode distance.

The computation specified in equation 1 will yield a scalar potential value $g(x, y)$ corresponding to every map coordinate x and y. This matrix, **g**, is plotted as a color coded 2D map representing the voltage distribution over the scalp at one particular time point.