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Brain-Computer Interface Technology for Neurorehabilitation

DOCTORAL THESIS

to achieve the university degree of

Doktorin der Naturwissenschaften

submitted to

Graz University of Technology

Supervisor

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Institute for Knowledge Discovery

Faculty of Computer Science and Biomedical Engineering

Graz, November 2015

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Abstract

Locomotor impairments represent one of the main factors preventing stroke survivors from leading an autonomous and self-determined life. A major motor rehabilitation goal is therefore that patients regain a certain level of functional gait. However, there is still no scientific consensus on the neural mechanisms underlying the recovery of lower limb functions. Brain-Computer Interfaces (BCI) may be a powerful tool for motor rehabilitation because they can decode motor intention and mental states from neurophysiological signals alone and capture information on brain activity related to the state of recovery.

In order to develop BCIs for gait rehabilitation, it is important to understand the cortical processes that are involved in human locomotion. Recent advances in signal processing methods have made it possible to counteract movement artefacts in the electroencephalogram (EEG) and to study neural correlates during actual gait.

The aim of this thesis was to investigate the electrocortical dynamics that accompany functional gait movements and hence contribute to the development and application of BCI technology for gait rehabilitation after stroke. Furthermore, this thesis aimed at investigating how well different training paradigms activate cerebral motor networks in healthy individuals. This measurement may help to infer the efficacy of certain therapy approaches. These problems were tackled using high-density EEG recordings and Independent Component Analysis (ICA) during robot assisted – and independent treadmill walking in able-bodied individuals.

Three studies were carried out as part of this thesis, covering different aspects of gait training. Since active participation and voluntary drive in a movement has been shown to be crucial for motor learning, study I compared active to passive gait movements in a robotic gait trainer. Study II investigated motor planning during walking in an interactive virtual environment. Given that motor impairments often affect the ability to adapt gait patterns, study III investigated neural correlates of gait adaptation strategies using a novel sensorimotor synchronization task.

These studies show that functional gait movements are represented in oscillatory electrocortical activity. Study I demonstrated that single gait cycle phases are reflected in low gamma band amplitude (25-40Hz) modulations over the premotor cortex. Furthermore the results suggest that mu and beta suppression over midline sensorimotor areas during steady-state gait and step adaptation reflect increased motor activation during human upright walking. Study II showed for the first time the involvement of mu and beta suppression in a premotor-parietal network in visuomotor integration during walking. Study III revealed that two distinct beta band oscillatory networks interplay in the service of gait adaptation – motor cortical beta desynchronization (13-35 Hz) reflecting motor readiness and frontal beta synchronization (14-20 Hz) related to cognitive top down control. Furthermore, a right frontal beta band power increase was modulated by task difficulty (step lengthening - easy vs. step shortening - difficult). This effect may reflect higher demand of cognitive control and inhibition related to movement-control during step shortening.

This thesis also shows the extent of cortical activation relative to different training strategies which may allow to infer the efficacy of certain therapeutic approaches. Study I shows that active participation in gait movements is represented by a desynchronization in the mu and beta band over

midline sensorimotor areas. Furthermore study II shows that interactive movement related feedback in a Virtual Environment (VE) compared to movement unrelated feedback decreases mu and beta rhythms in premotor and parietal areas during robot assisted gait, suggesting stronger activation of these areas. This indicates that the interactive feedback task increases voluntary motor drive during walking. Interestingly the interactive feedback task was associated with higher activation of the right parietal lobe – an area that has been connected to the feeling of agency. The experience of agency is generated by the perception of changes in the environment caused by our actions and also plays a role in motor learning. The results of these studies provide the first neurophysiological evidence that goal and task oriented training paradigms promote the active motor planning of gait movements and thus may stimulate and enhance motor learning during the therapy.

This thesis provides an exemplary framework for future electrophysiological paradigms to study movement disorders and their recovery. The results show that cortical excitability during gait training can be determined through neuronal oscillations. This measurement may be used in clinical settings to assess the activation of cortical motor networks and identify neural correlates of plasticity. The results further demonstrate the functional significance of electrocortical oscillations in gait movements. These findings contribute to the fundamental knowledge about cortical control in gait movements and may lead to a better understanding of cortical recovery and reorganization during locomotor therapy.

Zusammenfassung

Motorische Gangstörungen nach dem Schlaganfall beeinträchtigen nachhaltig die Lebensqualität der Betroffenen durch Einschränkung von Autonomie und Selbstbestimmtheit im Alltag. Das Erreichen eines gewissen Grades funktionaler Gehfähigkeit ist deshalb ein entscheidender Faktor in der motorischen Rehabilitation. Es ist jedoch unklar, welche Trainingsstrategien die rehabilitationsinduzierte Plastizität in Bezug zu Gangbewegungen bestmöglich fördern.

Brain-Computer Interfaces (BCIs) erlauben die Erkennung von Bewegungsintention und mentalen Zuständen durch die Ableitung neuroelektrischer Aktivität von der Kopfoberfläche. Der Einsatz von BCIs im Bereich der Rehabilitation von Schlaganfall ist vielversprechend, da diese Systeme rehabilitationsinduzierte Änderungen der Gehirnaktivität rückmelden, und so neuronale Korrelate plastischer Veränderungen erfassen könnten. Um BCIs für die Gangrehabilitation zu entwickeln, ist jedoch ein grundlegendes Verständnis der in den menschlichen Gang involvierten kortikalen Prozesse erforderlich.

Die Anwendung von BCI Technologien während der Gangrehabilitation ist besonders herausfordernd, weil Bewegungsartefakte Störungen im Elektroenzephalogramm (EEG) verursachen können. Aus diesem Grund werden in aktuellen Studien meist nur einzelne Teile von Bewegungsabläufen untersucht. Jüngste Fortschritte im Bereich der Signalverarbeitungsmethoden ermöglichen die Untersuchung neuronaler Korrelate des aufrechten Gehens mithilfe von Quellentrennverfahren.

Das primäre Ziel dieser Arbeit ist die Untersuchung der kortikalen Kontrolle von funktionalen Gangbewegungen, um ein umfassenderes Bild der Gehirnfunktionen in Bezug zu komplexen Bewegungsabläufen zu erlangen. Ein weiteres Ziel betrifft die Erforschung kortikaler Aktivierung in Relation zu verschiedenen Trainingsstrategien, um die neuronale Wirkung von Rehabilitationsverfahren zu evaluieren. Dieses Wissen könnte für einen gezielteren Einsatz von derartigen Interventionen in der Neurorehabilitation genutzt werden, welche Informationen über den Zustand des Gehirns berücksichtigen.

In drei Studien wurden verschiedene Aspekte des Gangtrainings mittels hochauflösenden EEG Aufnahmen und Independent Component Analysis während robotergestütztem- und unabhängigem Gehen auf einem Laufband untersucht. Da aktive Bewegungsplanung kritisch für motorisches Lernen ist, wurde in Studie I aktives und passives Gehen in einem robotergestützen Gangtrainer untersucht. Studie II untersuchte die motorische Planung während dem Gehen in einer interaktiven, virtuellen Umgebung. Die Fähigkeit unser Gangmuster an Veränderungen in der Umwelt anzupassen ist oft durch motorische Störungen nach dem Schlaganfall beeinträchtigt, was zu einem erhöhten Sturzrisiko führt. Um die kortikale Steuerung von Gangkorrekturen zu untersuchen, wurden Teilnehmer in Rahmen von Studie III instruiert, ihre Schritte an Veränderungen im Tempo einer rhythmischen auditorischen Sequenz anzupassen (längere und kürzere Schritte).

Die Ergebnisse dieser Arbeiten geben Hinweise auf die funktionale Rolle von neuroelektrischen Oszillationen in Zusammenhang mit Gangbewegungen. Studie I zeigte, dass einzelne Gangphasen in Amplitudenmodulationen des unteren Gamma Bandes (25-40Hz) über dem prämotorischen Kortex abgebildet sind. Darüber hinaus beweisen die Ergebnisse, dass rhythmisches und adaptives Gehen zu

einer Unterdrückung von Mu- und Beta Band Oszillationen in sensomotorischen Arealen führt. Dieser Effekt kann als eine gesteigerte Aktivierung des motorischen Systems während dem menschlichen aufrechten Gang verstanden werden. Studie II zeigte zum ersten Mal die Beteiligung von Mu- und Beta Band Desynchronisation in einem prämotorisch-parietalen Netzwerk in der visuomotorischen Integration beim Gehen. Studie III gibt Hinweise auf die Rolle zweier oszillatorischer Beta Band Netzwerke in der Anpassung des Gangmusters: Motorische Beta Band Desynchronisation (13-35 Hz) in Bezug zu motorischer Bereitschaft und frontale Beta Band Synchronisation (14-20 Hz) in Verbindung mit kognitiver top-down Kontrolle. Zusätzlich erhöhte die Schwierigkeit der Bewegungsaufgabe die Beta Band Leistung im rechten Frontallappen (längere Schritte leichter, kürzere Schritte schwieriger). Dieser Effekt spiegelt vermutlich die erhöhte kognitive Kontrolle während Schrittverkürzungen wieder.

Die Arbeit zeigt auch das Ausmaß kortikaler Aktivierung in Relation zu verschiedenen Trainingsansätzen und könnte somit Hinweise auf deren Effektivität geben. Studie I zeigt, dass aktive Teilnahme an Gangbewegungen sich in einer Desynchronisation von Mu- und Beta Band Rhythmen in zentralen sensomotorischen Arealen wiederspiegelt. Studie II weist nach, dass Gehen in einer interaktiven virtuellen Umgebung die Aktivierung (Desynchronisation von Mu- und Beta Rhythmen) in prämotorischen und parietalen Arealen, im Vergleich zu Feedback ohne Bezug zur Bewegung, signifikant steigert. Dies weist darauf hin, dass die interaktive Feedback Aufgabe motorische Planung während dem Gehen erhöht. Interessanterweise wies die interaktive Feedback Aufgabe auch eine höhere Aktivierung im rechten Parietallappen auf, der in Verbindung mit *Agency* gebracht werden kann. Das Gefühl von *Agency* entsteht durch den wahrgenommenen Effekt unserer Aktionen auf unsere Umwelt, und dieser Mechanismus spielt auch bei motorischem Lernen eine Rolle. Die Ergebnisse beider Studien liefern erste neurophysiologische Hinweise, dass ziel- und aufgabenorientierte Trainingsparadigmen aktive motorische Planung von Gangbewegungen fördern, und somit einen besseren motorischen Lerneffekt in der Therapie erzielen könnten.

Zusammengefasst ist diese Forschungsarbeit relevant für den Bereich der Neurorehabilitation, denn sie zeigt, dass kortikale Aktivierung während dem Gangtraining anhand von neuroelektrischen Oszillationen erfasst werden kann. Die Ergebnisse belegen zudem, dass Gangbewegungen durch die Modulation von neuronalen Rhythmen beschrieben werden können. Diese Erkenntnisse tragen zum Grundlagenwissen der Gehirnfunktionen in Beziehung zu funktionalen Gangbewegungen bei, und können so zu einem verbesserten Verständnis von kortikaler Erholung und Reorganisation während der Gangrehabilitation führen.

Diese Dissertation hat darüber hinaus gezeigt, dass durch Quellentrennverfahren kortikale Aktivität von mechanischen Störungen und Muskelaktivität im EEG getrennt werden kann, und so neuronale Korrelate während dem aufrechten Gehen untersucht werden können. Dieser Aspekt ist vor allem auch für die klinische Forschung relevant, da durch die Überwachung der Gehirnaktivität während der Therapie, Korrelate neuronaler Plastizität untersucht und identifiziert werden können. Dies dient der Entwicklung von neurowissenschaftlich informierten motorischen Therapien.

Aknowledgements

I want to express my gratitude to all the people who directly or indirectly made it possible for me to finish this thesis.

Thank You,
Christa Neuper for supervising my thesis and for the support and precious advice throughout this time.
Gernot and **Reini** for giving me the possibility to work on interesting research projects at the BCI lab at TU Graz but also the freedom to work on my own ideas, and for the advice and support during my PhD
Teo, for being my friend and teaching me all the signal processing stuff, it was a pleasure to work with you
Clemens for discussions about statistics and all the help with my grant proposals
Martin (the tall one) for all the great conference trips, and discussions about oscillations stuff
Everyone working at the Graz BCI lab, for fruitful scientific discussions, horror movie nights and great hikes.
Scott for giving me a different perspective on how to look at the data and think about the brain
All the people at the Swartz Center for Computational Neuroscience at UCSD
Ramon for being part of my life, and of course to **my family** that always supported me during this time.

Abbreviations

ANOVA	Analysis of Variance
AMICA	Adaptive Mixture Model Independent Component Analysis
BA	Brodmann Area
BCI	Brain-Computer Interface
BEM	Boundary Element Model
COA	Cue Onset Asynchrony
CSP	Common Spatial Patterns
dlPFC	Dorsolateral Prefrontal Cortex
ECG	Electrocardiogram
ECoG	Electrocorticogram
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculogram
ERD	Event-Related Desynchronization
ERDS	Event-Related Desynchronization and Synchronization
ERP	Event-Related Potential
ERS	Event-Related Synchronization
ERSP	Event-Related Spectral Perturbation
FES	Functional Electrical Stimulation
FIR	Finite Impulse Response
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
IC	Independent Component
ICA	Independent Component Analysis
L	Left
LFP	Local Field Potential
LH	Left Heelstrike
MEG	Magnetencephalography
MI	Mutual Information
MNI	Montreal Neurological Institute
MoBI	Mobile Brain-Body Imaging
MRCP	Motor Related Cortical Potential
muV	Microvolt
PCA	Principal Component Analysis
PPC	Posterior Parietal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PSD	Power Spectral Density
R	Right
RH	Right Heelstrike

SCP	Slow Cortical Potential
SD	Standard Deviation
SMA	Supplementary Motor Area
SMR	Sensorimotor Rhythm
SOBI	Second Order Blind Identification
SPECT	Single-Photon Emission Computed Tomography
StOA	Step Onset Asynchrony
TMS	Transcranial Magnetic Stimulation
VE	Virtual Environment

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1. Introduction

Rhythmic movements such as walking, running and swimming are defined by fluent and counterbalanced movements that allow to explore the environment and permit quick sensorimotor adaptations. For this reason, locomotion has been previously portrayed as 'the silent music of the body' (Harvey, 1627, quoted in Sacks, 2004). In pathological gait disorders such as stroke, this effortless, smooth stream of movements is disturbed.

Locomotor impairments after stroke are typically expressed by marked asymmetries in the gait pattern. Gait parameters such as speed, cadence, stride length, endurance and symmetry of gait are affected in stroke patients. Besides impairments in the regularity of the gait pattern affected individuals also have difficulties to adapt their steps to variations in the environment. This results in a reduced ability to avoid obstacles (e.g., den Otter et al., 2005) and an increased risk of falls (e.g., Weerdesteyn et al., 2006). Therefore, stroke survivors rarely reach a level of functional gait (Perry & Davids, 1992) i.e. the ability to walk safely and independently at an acceptable speed, and hinders affected individuals to perform every day activities autonomously (Duncan et al., 1998).

Consequently, gait impairment is a major goal in post-stroke rehabilitation and has been one of the most investigated topics in studies on neurological gait disorders. Recovery of gait related motor functions can only be maximized by a fundamental understanding of the normal mechanisms of gait control in healthy individuals and anomalies in pathological gait.

1.1. Rehabilitation of motor impairment

Stroke lesions are a result of oxygen deprivation due to an interruption of blood flow, causing cell death in the affected brain area. Most commonly this is caused by a blood clot (arterial ischemia) or when a blood vessel bursts (hemorrhage) resulting in a flow of blood into parts of the brain. The location of the stroke lesion also determines the nature of impairments, i.e. motor dysfunctions may be associated with damage in sensorimotor areas.

Restoration of neurological impairments is a complex process comprising spontaneous and functional recovery. The mechanisms of spontaneous recovery are not yet fully understood but are thought to be related to spontaneous rewiring, sprouting and branching processes of neurons in the area surrounding the stroke lesion (Ueno et al., 2012). External factors such as motor behavior seem to have no impact on these processes. Spontaneous recovery after stroke generally occurs within the first 3-6 months and has a predictable timecourse, with a rapid initial improvement of cognitive and motor functions and a negative acceleration with time (Skilbeck et al., 1983). Functional recovery is related to cortical reorganization and is of special interest as it can be guided by the principles of motor learning Nudo (2003).

In the healthy animal brain, motor skill acquisition is associated with morphologic changes to the motor cortex (Diamond et al., 1964, Greenough et al., 1985, Kleim et al., 1996, Rosenzweig et al., 1964). In fact, functional reorganization of the rat (Kleim et al., 1998) and monkey (Plautz et al., 2000) motor cortex occurs not simply relative to simple repetitive movement but only relative to the

development of skilled forelimb use. Nudo (2003) proposed that plastic changes related to motor learning share the same functional mechanisms on the neuronal level as post-stroke recovery of motor functions. Indeed, recent research in humans has identified two main properties that promote neural plasticity in motor skill acquisition during gait training: 1) intensity of the training (Langhorne et al 2009) and 2) problem-solving in functional tasks to achieve a behavioral response, (Adkins et al., 2006, Liepert et al., 2000, Van Peppen et al., 2004; Salbach et al., 2004). In contrast, training that is focused on single parts of movements such as muscle strengthening and muscular re-education, fails to generalize to functional tasks and activities (Van Peppen et al., 2004).

Assisted over ground walking is the main intervention in current physical gait rehabilitation therapies. This approach requires that physical therapists manually control the lower limb position of motor impaired individuals. Functional gait movements have been shown to improve with assisted over ground - and treadmill training in combination with body weight support (Moseley et al., 2005). However, the number of movement repetitions is restricted in this form of therapy due to the physical load placed on the therapist. In the last decade robotic devices have been introduced for people with mild to severe motor impairments in gait rehabilitation. These devices can provide task oriented training while enabling a large number of movement repetitions (Brütsch et al., 2010; 2011, Schuler et al., 2011). In a later stage of recovery other approaches suggest to use external rhythms to improve timing aspects of gait movements. It has been shown that gait parameters such as speed, cadence, stride length, and symmetry of gait, can be improved with training using auditory cues compared to other state of the art rehabilitation approaches (Hurt et al., 1998, Roerdink et al., 2007, Thaut et al., 1997; 2007).

However, there is no clear evidence that one rehabilitation approach is more effective than another in promoting cortical reorganization and consequently functional gait after stroke (Pollock et al., 2007). Recently, it has been proposed to pursue a so-called top-down approach in gait rehabilitation (Belda-Lois et al., 2011), that aims at designing rehabilitation therapies relative to the state of the brain after stroke. A technology which may open up a window to information on cortical changes in stroke patients and the cerebral activation patterns relative to different therapy approaches is the brain-computer interface (BCI).

1.2. Brain-computer interfaces for post-stroke rehabilitation

Brain-computer interfaces (BCI) can measure and decode motor intention and mental states from neurophysiological signals. Therefore, BCIs might be a powerful tool for motor rehabilitation, because they can capture and transfer information on brain activity related to the state of recovery (Pfurtscheller & Neuper, 2006; Dobkin et al., 2007; Birbaumer et al., 2008; Daly and Wolpaw, 2008).

Traditional BCI-based approaches have proposed to use mental simulation of movement, to promote motor learning in post-stroke rehabilitation (Daly and Wolpaw, 2008). Mental imagery of movements shows similar patterns to motor execution in primary- and pre-motor areas and represents a safe way to practice movements even in the absence of residual motor function. There is some evidence that motor imagery of lower limb movements such as dancing or foot sequences can help to improve gait (Dickstein et al., 2004; 2007). Motor imagery can also be paired with sensory stimulation of the

affected limb. In this approach motor imagery is commonly used to control an assistive device or activate electric stimulation of the muscles for moving the affected limb. This pairing of motor and sensory activation is thought to enhance cortical plasticity by Hebbian principles. Indeed, a recent study has shown that precise temporal pairing of imagery of motor evoked potentials and muscle stimulation increases cortical plasticity as assessed by cortical excitability through TMS (Mrachacz-Kersting et al., 2012).

BCIs can be also used to measure the current state of the brain after stroke (Belda-Louise et al., 2011, Kaiser et al., 2012) and convey information about the patients' activation patterns in cortical motor networks during the therapy. This would allow to relate changes in cortical activity to functional gait improvements and provide a means to evaluate the effects of therapeutic interventions. However, in order to develop BCIs for gait rehabilitation, fundamental research investigating the neural dynamics during locomotion is critical to determine the role of cortical involvement in gait control.

1.3. Locomotion

1.3.1. Description of the Gait Cycle

Human gait is composed of a sequence of symmetric recurrent movements. One gait cycle is defined as the execution of two full steps starting and ending with the initial contact of the right heel so that a left heel strike marks the 50% of the gait cycle (see Figure 1). According to Perry & Davids (1992) the gait cycle is comprised of stance (0 to 60% of the gait cycle) and swing phase (60 to 100% of the gait cycle). The stance phase of gait divides into four stages: Loading response (0 to 10%), midstance (10 to 30%), terminal stance (30 to 50%) and preswing (50 to 60%) phases. The swing phase consists of three segments: Initial swing (60 to 73%), midswing (73 to 87%) and terminal swing (87 to 100%) phases.

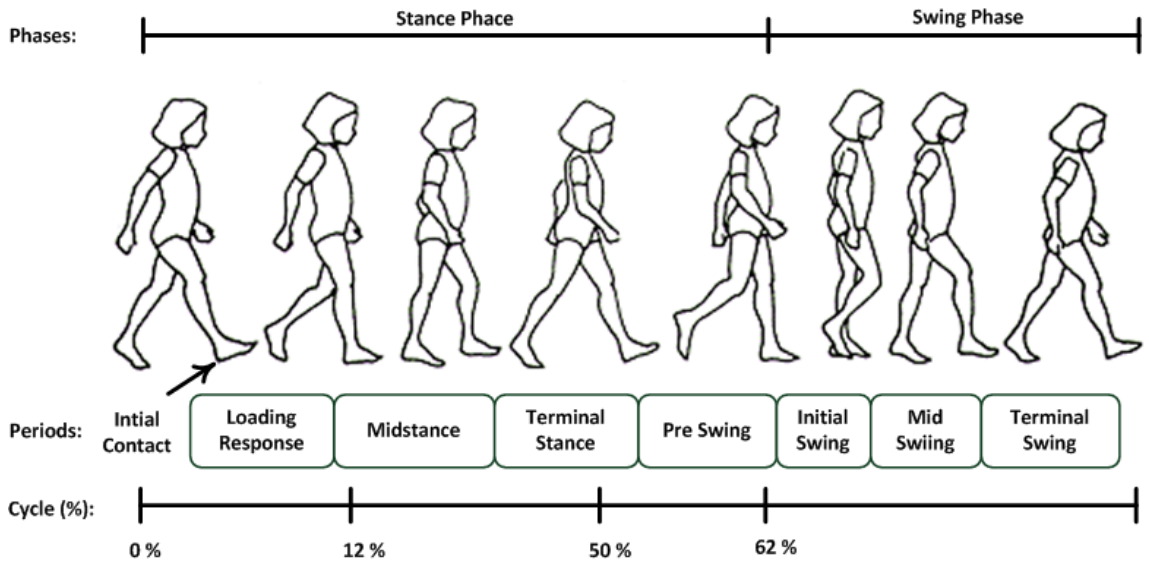

Figure 1.1. Gait cycle phases *(Perry, 1992, http://www.clinicalgaitanalysis.com/history/modern.html)*

Each cycle is initiated by a right heel strike which marks the beginning of the stance phase. The center of gravity of the body is shifted forwards so that the body weight progressively moves from the heel to the ball of the foot.
The swing phase is initiated when the toes leave the floor and proceeds by advancing the limb forward until terminating when the heel hits the ground. Each gait cycle incorporates two periods of double limb support occurring at the beginning and at the end of the stance phase of the right leg.

1.3.2. Neural correlates of gait

Central Pattern Generator: To accomplish the complex sequence of movements during stepping, extensor and flexor muscles moving the hip, knee and ankle joints are activated in an alternating pattern. A central pattern generator in the spinal cord has been proposed to produce this characteristic muscle pattern of stepping (Grillner, 1985; 2006). The central pattern generator receives input through sensory afferences on cutaneous reflexes, limb loading and hip position and can directly regulate the stepping pattern through this information (Duysens et al., 2000, Pang et al., 2000, Dietz et al., 2002).

Studies in decerebrate cats and rodents suggest that central pattern generators involved in locomotion are partly controlled by efferent input from regions in the brainstem and cerebellum (Armstrong, 1986, Drew et al. 1996, Rossignol et al. 2006). Human gait is assumed to be produced by the interaction between spinal central pattern generators and supraspinal cortical and subcortical structures (Van Hedel & Dietz, 2010, Dietz, 2003, Drew & Marigold, 2015).

Supraspinal control of gait: Recent evidence on the cortical contribution to walking in humans comes from a number of neuroimaging studies. Functional neuroimaging of gait poses practical problems, since techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) constrain participants to a lying position with fixated head in the scanner. Furthermore fear of movement artefacts in neuroimaging methods such as fMRI, magnetoencephalography (MEG) and electroencephalography (EEG) has led to experimental paradigms in which participants have to maintain artificially static positions. Few studies have therefore ventured the undertaking to investigate direct neural correlates during actual gait in humans. Prior research has mainly extrapolated findings on restricted movements e.g., leg or foot movements that represent a part of human locomotion to models of cortical and subcortical control of human gait (Dobkin et al., 2004, Luft et al., 2005, Metha et al., 2009, Müller-Putz et al., 2007, Neuper and Pfurtscheller, 2001, Pfurtscheller et al., 1997, Raethjen et al., 2008, Sahyoun et al., 2004, Wieser et al., 2010).

Studies measuring hemodynamic brain activity during pedaling and ankle dorsiflexion have shown a higher activation during active compared to passive movements in central primary sensorimotor and premotor areas (Christensen et al., 2000, Hollnagel et al., 2011, Dobkin et al., 2004; Sahyoun et al., 2004). Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have measured and compared brain activity before and after walking (Fukuyama et al., 1997, Hanakawa et al., 1999, la Fougere et al., 2010). These studies report that the premotor cortex, parietal cortex, basal ganglia and cerebellum in addition to medial primary sensorimotor areas seem to be involved in the supraspinal control of gait.
Cortical activity during gait initiation and precision stepping has been investigated by several fNIRS

studies. During gait adaptation (Suzuki et al., 2004) and motor preparation of gait (Suzuki et al., 2008, Koenraadt et al., 2013) the authors observed increased activity over the prefrontal cortex (PFC) and the supplementary motor area (SMA). Another study showed that walking compared to single foot movements increases activity bilaterally in the central primary sensorimotor area and the SMA (Miyai et al., 2001).

Electrophysiological studies have reported electrocortical potentials related to assisted lower limb movements (Wieser et al., 2010), and coherence between the EEG signal over Cz which is located over the foot area of the primary motor cortex and muscles of the foot **(**Raethjen et al., 2008**)**. A greater event-related desynchronization (ERD) (Pfurtscheller and Lopes da Silva, 1999) has been observed in the mu band relative to active vs. passive foot movement over midline sensorimotor areas (Müller-Putz et al., 2007). Mu (8 to 13 Hz) to beta (15 to 25 Hz) band ERD in the motor system has been related to the activation of sensorimotor areas (Crone et al., 1998, Pfurtscheller and Lopes da Silva, 1999, Neuper and Pfurtscheller, 2001, Pfurtscheller et al., 2003, Miller et al., 2007), while event related synchronization (ERS) in these bands has been associated with a deactivation or inhibition in the sensorimotor system (Klimesch et al., 2007, Neuper et al., 2006).

Recent EEG studies suggest that these principles can be extrapolated to whole body movements such as gait. Decreased alpha and beta band power over the foot motor area has been shown relative to assisted stepping movements in an upright position compared to periods of rest in a lying position (Wieser et al., 2010). Advances in signal processing methods have spawned a new research field called mobile brain body imaging (MoBI) aiming at the neuroimaging of whole body movements during natural behavior with EEG (Makeig et al., 2009). Several studies have emerged from this new approach showing for the first time the analysis of EEG during actual gait (Gwin et al., 2010; 2011, Presacco et al., 2011). Importantly, Presacco et al. (2011) reported a suppression of alpha band power during precision walking compared to standing. These electrophysiologic principles seem to extend also to subcortical structures. Singh et al. (2011) performed human local field potential (LFP) recordings from the basal ganglia during walking and found that power in low (4 to 12Hz) and high (60 to 90Hz) was significantly increased while beta band power (15 to 25Hz) was significantly decreased during walking compared to sitting or standing.

A few studies have also shown gait cycle related electrocortical and subcortical dynamics during walking. Fitzsimmons et al. (2009) were able to predict the kinematics of bipedal walking in monkeys by decoding of invasive recordings in sensorimotor cortex. Interestingly Singh et al. (2011) showed a gait related modulation of theta-alpha band power (6 to 11 Hz) in human LFP from the basal ganglia. Gwin et al. (2011) has shown broad band frequency modulation in the human EEG relative to the gait cycle during treadmill walking. The authors demonstrate that the method of independent component analysis (ICA) is able to decompose the EEG in artifact, muscle, and brain sources and allows to model cortical dynamics during whole body movements (Gwin et al., 2010; 2011, Gramann et al., 2010).

2. Methodological considerations

Brain-imaging methods such as fMRI or MEG require that participants remain motionless in a sitting or lying position and are highly susceptible to movement artefacts. The method of EEG in combination with sophisticated source separation analysis allows to overcome these limitations (Baillet, 2001, Michel, 2004, Makeig et al., 2009). EEG is the only non-invasive neuroimaging method that combines 1) mobile, low weight sensors that allow for head and body movements in ambulatory conditions and 2) a temporal resolution fine enough to analyze temporal brain dynamics relative to single gait cycle phases. In addition EEG allows to uncover different elements of cortical motor and cognitive control by investigating frequency-specific functions of neuroelectric oscillations. (Pfurtscheller et al., 2003, Buzáki and Draguhn, 2004, Neuper et al., 2006, Siegel et al., 2012).

2.1. Generation of the EEG

EEG is generated by the coordinated activity of a large number of neurons in the cortex (Luck, 2005, Buzaki, 2006, Kandel et al., 2013). On the single cell level, e.g. excitatory synapses of a neuron induce a current inflow to the cell (sink) at the apical dendrites and a current outflow (source) at the cell body. This flow of current causes a voltage difference between the sites of current influx (sinks) and current outflux (sources) to the cell and generates a tiny dipole in the extracellular space around the neuron. The linear sum of these overlapping dipoles or voltage fields, produced by the interaction of a large number of neurons, can be measured as the local field potential invasively or from the scalp (Buzaki, 2006).

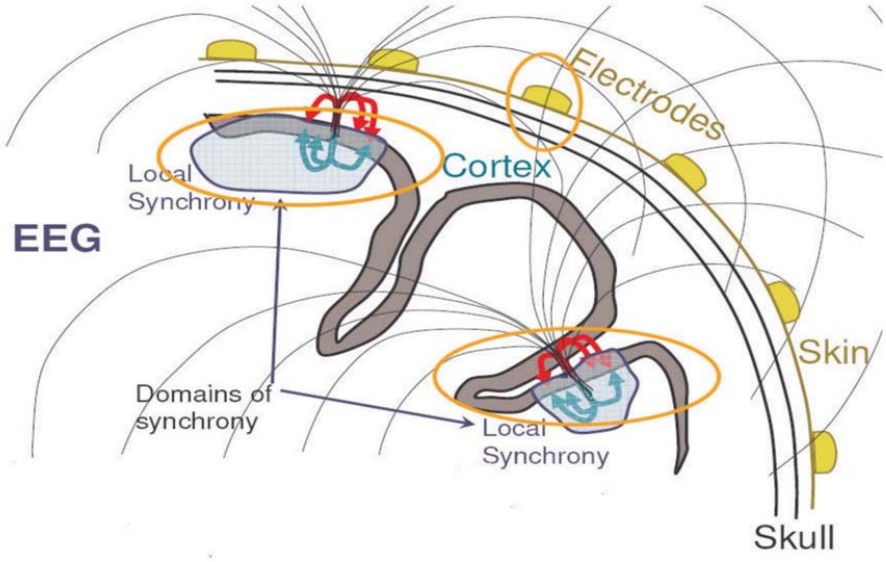

Figure 2.1. The EEG is a linear sum of voltages: *Different cortical sources project to the scalp and produce a linear sum of voltages at scalp sensors. (Makeig, 2005, Onton et al, 2006), (http://sccn.ucsd.edu/mediawiki/images/a/a8/EEGLAB2010_SM_mining_brain_dynamics_I.pdf).*

We can assume that many patches of neurons in different parts of the cortex are simultaneously active and generate electrocortical potentials that project and sum at the scalp. Due to the basic law of voltage conductance these electrocortical potentials spread out as they travel through tissues, cortex, the skull and the scalp (Nunez & Srinivasan, 2006). The voltage deflections we can measure at the scalp are therefore a mixture of relatively independent far field potentials generated in different parts of the cortex (Onton et al., 2006, Onton & Makeig, 2006, Buzaki, 2006) (see Figure 2.1).

Recovery of the location and orientation of the neural field generators underlying the EEG based on the spatially averaged activity detected by the scalp electrodes is limited due to the under-completeness of the inverse problem. This under completeness is given due to the fact that the inverse problem does not have a unique solution and any number of brain source configurations can produce an observed voltage distribution at the scalp (Luck, 2005, Buszaki, 2006, Nunez & Srinivasan, 2006)

2.2. EEG rhythms

The mean field (EEG) resulting from the summed collective behavior of neurons is a mixture of rhythms. Different oscillatory bands, involving frequencies from 0.1 Hz to 1000 Hz are generated by neuronal networks in the human cortex (Buszaki, 2006, Scheer et al., 2011, Fedele et al, 2012, Nikulin et al., 2014). These neuronal oscillators are linked to the much slower metabolic oscillators (Buszaki, 2006, Nikulin et a.l, 2014).

Following Berger's discovery and denomination of the EEG alpha rhythm in 1929, the later observed and distinguished frequency bands were named according to the Greek alphabet: delta, 0.5 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 12 Hz; beta, 12 to 30 Hz; gamma, >30 Hz. There is evidence that distinct frequency bands have different functional roles in motor and cognitive processing (Klimesch, 1999, Pfurtscheller et al., 1997, Curio, 2000, Neuper et al., 2006, Buzsaki, 2006), however studies also show that the exact boundaries between the different bands overlap and vary across participants, tasks and brain areas (Buszaki, 2006, Neuper et al., 2001, Andrew & Pfurtscheller, 1997, Pfurtscheller et al., 2000). Motor behavior for example has been connected mainly to alpha/mu (8 to 12Hz) to beta (13 to 30Hz) and gamma (30 to 200Hz) rhythms (Crone et al., 1998, Pfurtscheller and Lopes da Silva, 1999, Neuper and Pfurtscheller, 2001, Pfurtscheller et al., 2003, Miller et al., 2007). The power spectrum of the oscillatory frequencies in the EEG has a 1/f, distribution meaning that higher frequency oscillations occur at smaller amplitudes and are harder to detect (Buzsaki, 2006, Miller et al., 2009).

However, the precise functional mechanisms of most cortical and subcortical oscillations are unknown. Buszaki (2006) proposed that our brain is not continuously processing information but sampling discrete segments of time. This is achieved by using oscillatory cycles that act as a temporal processing window marking the beginning and the end of the encoded signal. Furthermore, information processing in the brain implies that information is transferred between brain areas. Since effective connectivity involves the synchronization of two cortical areas in a certain frequency band the period length of oscillations determines how far information can be transferred by one cycle. Thus information transfer between distant neuronal groups needs more time and therefore recruits slow oscillations whereas local processing involves fast oscillations (von Stein & Sarnthein, 2000, Libet et al., 2004, Buszaki, 2006).

2.3. Independent Component Analysis

Blind source separation with Independent Component Analysis (ICA) is a powerful approach to separate electric potentials composing the EEG (Makeig et al., 1996). ICA assumes the temporal independence of electrophysiological sources underlying the EEG signal and performs a linear data decomposition that parses multichannel EEG data into independent source signals.

2.3.1. Theoretical considerations

ICA, was originally developed for technical signal processing (Comon, 1994, Bell & Sejnowski, 1995). Infomax ICA is a specific type of ICA and has been applied to EEG data the first time by Makeig in 1996. Infomax ICA belongs to a group of methods that performs blind source separation by unmixing linearly summed signals.

A well-known problem in audio speech processing that can be solved with blind source separation methods is the cocktail party dilemma: assuming we have two persons s1 and s2 speaking simultaneously and two microphones x1 and x2 recording both voices.
The signals recorded at the microphones are a mixture of the two voices and can be expressed as (Comon, 1994, Lee et al., 2000):

$$X_1(t) = a_{11}s_1(t) + a_{12}s_2(t) \qquad (1.1)$$
$$X_2(t) = a_{21}s_1(t) + a_{22}s_2(t)$$

which can be formulated in matrix form as

$$X = A \times S \qquad (1.2)$$

Where X are the signals recorded at the microphones, S are the underlying voice sources and A is the mixing matrix (Comon, 1994, Lee et al., 2000). In theory S can be obtained by

$$S = A^{-1} \times X \qquad (1.3)$$

However, since A is unknown we need to solve the unmixing matrix W (the inverse of A) to recover the original sources. This can be done by blind source separation.

EEG measurement poses a similar dilemma as the cocktail party problem, since the sensors at the scalp record a linear overlay of independent sources (Lee et al., 2000, Hyvärinen & Oja, 2000, Palmer et al., 2006):

$$X(t) = a_1s_1(t)+a_2s_2(t)+\ldots+a_ns_n(t) = AS(t) \qquad (1.4)$$

Where X is the EEG signal and s are the underlying sources. Infomax ICA learns an unmixing matrix W that maximizes the independence of the sources (see Figure 2.1).

$$U = W \times X \qquad (1.5)$$

W is a $n \times n$ matrix while X and U are $n \times t$ matrices. The IC activations (U) are the independent source signals underlying the EEG. The independence of two events A and B is defined as:

$$P(A \text{ and } B) = P(A)P(B) \quad (1.6)$$

The two events are independent if the product of the probability of A and B occurring individually equals the probability of both occurring. Independence is a more powerful characteristic than uncorrelatedness. If the mean of the product of two random variables X and Y equals the product of the means, X and Y are uncorrelated (Hyvärinen & Oja, 2000).

$$E\{XY\}=E\{X\}E\{Y\} \quad E\{(X-mean(x))(Y-mean(y))\}= 0 \quad (1.7)$$

Two independent events are always uncorrelated however uncorrelatedness does not imply independence. A measure that can be used to determine independence is Mutual Information (MI) (Cover & Thomas, 1991, Lee et al., 2000, Hyvärinen & Oja, 2000). MI equals zero only when two events X and Y are independent.

$$MI(X,Y) = D(px,y(x,y) \,||\, px(x)py(y)) >= 0 \quad (1.8)$$

Infomax ICA maximizes independence of the resulting sources by minimizing their mutual information. Infomax ICA can only uncover the same number of sources as there are recording sensors (Bell & Sejnowski, 1995, Lee et al., 2000, Hyvärinen & Oja, 2000).

The studies in this thesis use an adaptive independent component analysis (ICA) mixture model algorithm [AMICA] to decompose the EEG (Palmer et al., 2006; Palmer et al., 2008). This is a generalization of the Infomax ICA algorithm (Bell and Sejnowski, 1995; Makeig et al., 1996). The original Infomax ICA method assumes the spatial stationarity of sources, however for electrocortical sources this may not always be true. A single source model may therefore not be sufficient to represent signals in non-stationary environments. AMICA allows to represent EEG sources with multiple models (Palmer et al., 2006).

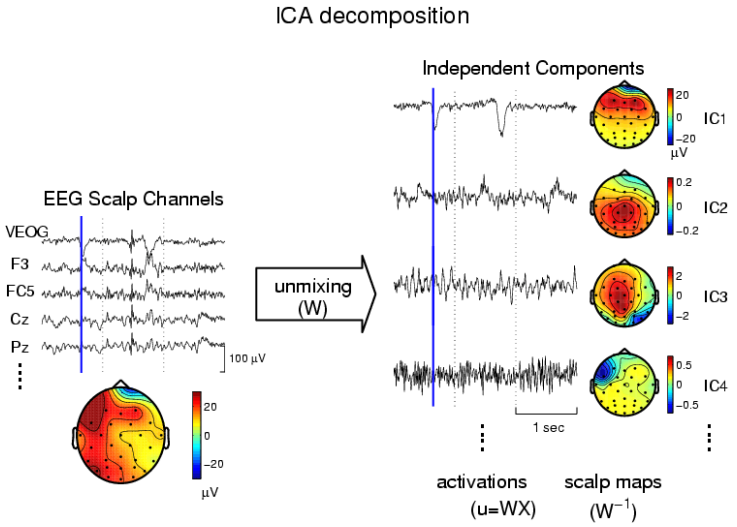

Figure 2.2. The observed EEG signal X represents a linear mixture of sources s*. ICA learns an unmixing matrix W. Multiplying W with the EEG signal X results in the maximally independent source timecourses (Y) (Jung et al., 2000).* (*http://sccn.ucsd.edu/eeglab/workshop06/handout/TP_Jung_Workshop06_ICA.pdf)*

2.3.2. Application of ICA to EEG

Outcomes of ICA decompositions and anatomic assumptions suggest that the cortical EEG sources uncovered by ICA can be interpreted as the waveforms of the original far field potentials projecting to the scalp (Onton et al., 2006). In fact, independent cortical sources have an associated scalp projection resembling that of a single equivalent dipole resulting from the synchronous local field activity in a patch of cortex (Delorme et al., 2012).

An ICA decomposition is valid as long as the properties of EEG dynamics coincide with the assumptions of the ICA model. Electric potentials underlying the EEG signals must exhibit relative temporal independence, mix linearly at scalp sensors and be spatially stationary (Makeig et al., 1996, Hyvärinen & Oja, 2000, Lee et al., 2000, Onton et al., 2006). The basic laws of volume conduction and studies showing the relative temporal independence between synchronuous activity in different patches of cortex support these assumptions (Salinas & Sejnowski 2001, Nunez & Srinivasan, 2006).

***Circumventing the under-completeness of the inverse model with ICA*:** Since the scalp projection of independent cortical EEG sources resembles that of an equivalent current dipole their location can be relatively unequivocally estimated. With standard inverse source modeling methods an equivalent current dipole can be calculated whose scalp projection provides the best fit relative to the observed scalp distribution (Onton et al., 2006). Different head models can be used to localize equivalent current dipoles. Due to their simplicity spherical head models that use only three layers of conductive tissue (cortex, skull and scalp) are widely used. However, it has been shown that more realistic head models that assume different layers within the cortex give more exact results (Oostenveld, & Oostendorp, 2002). It has to be taken into consideration however that the EEG has a low spatial resolution (about 1-2cm) and can measure only cortical surface activity. Thus the locations of estimated dipoles have to be interpreted with caution.

In the studies of this thesis a standard boundary element (BEM) model (Gramfort et al., 2010) using an anatomical template colin27 / MNE brain (Collins, 1994) has been utilized which employs the method of finite element models. In the BEM the brain is divided into segments assuming different resistance and conductance properties for separate compartments of tissue (Luck, 2005).

Homogenous source activity over subjects: EEG signals recorded at any scalp sensor contain the summed activity from multiple cortical and non-cortical processes in different parts of the cortex (Nunez & Srinivasan, 2006). In traditional EEG research comparisons across subjects are generally made according to electrode locations. For example in many EEG studies brain activity relative to right hand movement has been generally compared using electrode location C3 (Pfurtscheller et al., 1997, 2000, Neuper & Pfurtscheller, 2001). However, each human cortex is uniquely folded and thus EEG sources of individual subjects may differ in size, strength and orientation (Onton et al., 2006). The same scalp sensor may therefore record different portions of cortical and non-cortical potentials over participants, making it impossible to determine which sources add up to the EEG signal (Onton et al., 2006). On the other hand separating the EEG into independent source signals allows to group truly similar source signals by comparing homogeneous collections of source scalp maps, locations and time course over subjects (Onton et al., 2006, Onton & Makeig, 2006).

2.4. Artefacts during gait

The EEG signals recorded at the scalp have a weak amplitude in the range of microvolts compared to electric noise and artefacts present at the scalp electrodes. Furthermore biological noise such as electric muscle activity (electromyogram- EMG), eye movements (electrooculogram - EOG) and heart electrical activity (electrocardiogram - ECG) have overlapping frequency ranges relative to the EEG.

Furthermore, due to the physical activity during walking participants are prone to start sweating which introduces slow drifts in the EEG recordings caused by the activation of sweat glands. Since these artefact signals exhibit relative temporal independence between each other and electrocortical sources they can be relatively easily separated with ICA (Jung et al., 2000, Delorme et al., 2007, Hoffmann & Falkenstein, 2008).

Additionally, recording of EEG during gait can be complicated by other sources of noise introduced by movement artefacts such as head movements, cable swinging and electrode movement. It has been shown that these motion artefacts are not limited to a restricted band of frequencies but overlap with the EEG frequency range. A study by Gwin et al., 2010 compared methods to remove motion artefacts in the EEG recorded during walking and running. The authors found that the EEG spectrum exhibits frequency peaks coinciding with the step frequency and its harmonics. Furthermore the authors demonstrate that during steady state walking the EEG signal is affected most considerably in the low frequencies below 4 Hz. Importantly the study shows that performing blind source separation with ICA on the EEG data they were able to separate movement artefacts, neurophysiological artefacts and electrocortical sources during walking (Gwin et al., 2010; 2011, Gramann et al 2012).

3. Aim of this work

Locomotor impairments hinder affected individuals to perform activities of daily living autonomously. Regaining a level of functional gait (Perry, 1992) is therefore an important goal in post-stroke motor rehabilitation. However there is little consensus on the mechanisms promoting gait recovery and the effectiveness of different rehabilitation approaches (Pollock et al., 2007). Brain-Computer Interfaces (BCI) provide the possibility to measure and translate brain activity during gait rehabilitation and would allow to relate cortical changes to functional improvements and to evaluate the efficiency of training approaches (Belda-Luis et al., 2011).

In order to develop BCIs for gait rehabilitation and improve rehabilitation therapies, it is crucial to understand the supra-spinal mechanisms involved in human locomotion. Complex movements such as gait require the precise temporal coordination of different body parts and the synchronization of these movements with events in the environment. The high temporal resolution of EEG recordings allows us to analyze electrocortical activity as it relates to single gait cycle phases and to sensory events that require the modification of the regular gait pattern. Yet, electrocortical dynamics during human upright walking are not well-studied (Gwin et al., 2010, Haefeli et al., 2011, Presacco, 2011) mainly due to concerns of movement artefacts in the EEG signal that occur during whole body movements. Recently it has been shown that with the application of advanced signal processing methods such as ICA (Gwin et al., 2010; 2011) it is possible to account for movement artefacts in the EEG signal.

The goal of this thesis was to model brain activity in the EEG relative to functional gait movements and identify novel features for the application of BCIs to motor rehabilitation systems. Since EEG rhythms such as mu, beta and gamma rhythms have been shown to be related to motor processing (Crone et al., 1998, Pfurtscheller and Lopes da Silva, 1999, Neuper and Pfurtscheller, 2001, Pfurtscheller et al., 2003, Miller et al., 2007) the studies of this thesis aimed at uncovering the role of these rhythms in steady state gait movements as well as the adaptation of steps to external changes. This knowledge is essential for studying motor impairment after brain injury and may help to identify novel features for the application of BCIs to motor rehabilitation systems. Finally, this thesis aimed at investigating neural correlates related to different training strategies to determine the efficacy of certain therapy approaches. This knowledge is important since there is no consensus on the effectiveness of different rehabilitation approaches and currently there is no way to determine how well affected individuals activate their cerebral motor networks during the gait training.

To approach these problems, this thesis concentrated on the analysis of neuronal oscillations obtained from high-density electroencephalographic (EEG) recordings in healthy participants during walking. ICA was used to separate brain and artefact sources. Three studies were carried out within the scope of this thesis:

1) Since active participation and voluntary drive are crucial for motor learning (Lotze et al., 2003), in the first study in this thesis the neural correlates of active participation in robot assisted gait training (Wagner et al., 2012) were examined. Goal was to explore novel features in the EEG for the development of a BCI that detects active engagement in gait movements. This study also

investigated the feasibility of recording EEG during automated gait training and examined neural oscillations related to single gait cycle phases.

2) Voluntary actions are important for motor learning and involve two different subjective experiences: the experience of intention, i.e. planning to do something and the experience of agency, which is the feeling that our actions have caused a particular event in the environment (Kaelin-Lang et al., 2005; Lotze et al., 2003). Therefore the second study in this thesis, investigated whether interactive movement related feedback in a Virtual Environment (VE) task increases voluntary motor drive and agency during robot assisted gait (Wagner et al., 2014).
3) A recent study demonstrated that stroke patients prefer longer step responses in gait adaptation to shorter step responses (Roerdink et al., 2009). Interestingly dual task paradigms during walking cause participants to take longer strides (Li et al., 2012; Lovden et al., 2008; De Sanctis et al., 2014) suggesting that voluntary deceleration of steps requires less cognitive resources (Varraine et al., 2000). The third study in this thesis therefore used rhythmic auditory cues during treadmill walking to study the underlying neural correlates of gait adaptation strategies (Wagner et al., 2015).

Chapter 4 provides a short summary of Study 1 and 2 (these studies are attached in published form to the thesis) and a detailed description of Study 3 and Chapter 5 provides a general discussion of the results and conclusions.

4. Methodology and results

4.1. STUDY I: Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able bodied subjects

Wagner, J., Solis-Escalante, T., Grieshofer, P., Neuper, C., Müller-Putz, G., & Scherer, R. (2012). *Neuroimage*, *63*(3), 1203-1211. *doi:10.1016/j.neuroimage.2012.08.019*

Post-stroke gait rehabilitation therapy aims at the functional recovery of gait movements by promoting cortical reorganization of the areas related to motor execution. Robotic gait trainers are increasingly used in locomotor rehabilitation as the repeated execution of the motor pattern of human locomotion is believed to reactivate supraspinal locomotor centers. Robot assisted gait training can lead to passive movements as it executes a constant force and does not adapt to motor contributions by the patient (Hidler and Wall, 2005; Israel et al., 2006). It has been previously shown that functional recovery of movements shares the same neuronal mechanisms as motor learning Nudo (2003) and that the active contribution in a movement is crucial for the encoding of motor memory (Lotze et al., 2003; Kaelin-Lang et al., 2005).

Prior studies have tried to assess patient participation using only indirect measures such as force, heart rate and oxygen uptake (Lünenburger et al., 2007, Koenig et al., 2011, Pennycott et al., 2010). We propose the direct assessment of active participation in gait movements based on the amount of cortical activation determined from the electroencephalogram. The measurement of electrocortical patterns during automated gait training however is challenging due to the contamination of the EEG signal with movement and muscular artefacts. Previously a study (Gwin et al., 2010) showed that it is possible to separate electrocortical and artifactual activity in the EEG with Independent Component Analysis during walking.

The aim of this work was to investigate the electrocortical patterns that accompany functional gait movements and establish the feasibility of measuring EEG during automated gait training. Furthermore, the study aimed at examining the neural correlates of active participation in the execution of locomotor movements. To this end we recorded high density EEG (120 sensors) from 15 participants and compared active and passive walking in a gait robot.

Major contributions: The study demonstrated that the recording of meaningful EEG signals during automated gait training is feasible and that active participation during gait training can be assessed directly based on neuronal oscillations. The study showed a significantly higher activation (desynchronization in mu and beta bands) in the sensory foot area during active compared to passive walking. It has been demonstrated in two further studies (Solis-Escalante et al., 2012; Wagner et al., 2014) that these findings can be used to detect active participation in gait movements on a single trial basis.

Furthermore, the study shows that gait movements can be described by cortical rhythms. We show for the first time that gait cycle phases are related to power modulations in the lower gamma band

(25 to 40Hz) over the premotor cortex. At the same time mu (7 to12Hz) and beta rhythms (15 to 22Hz) are suppressed during walking compared to standing. This study is the first to provide evidence that the functional role of mu and beta rhythms in the motor cortex is valid also for functional gait movements.

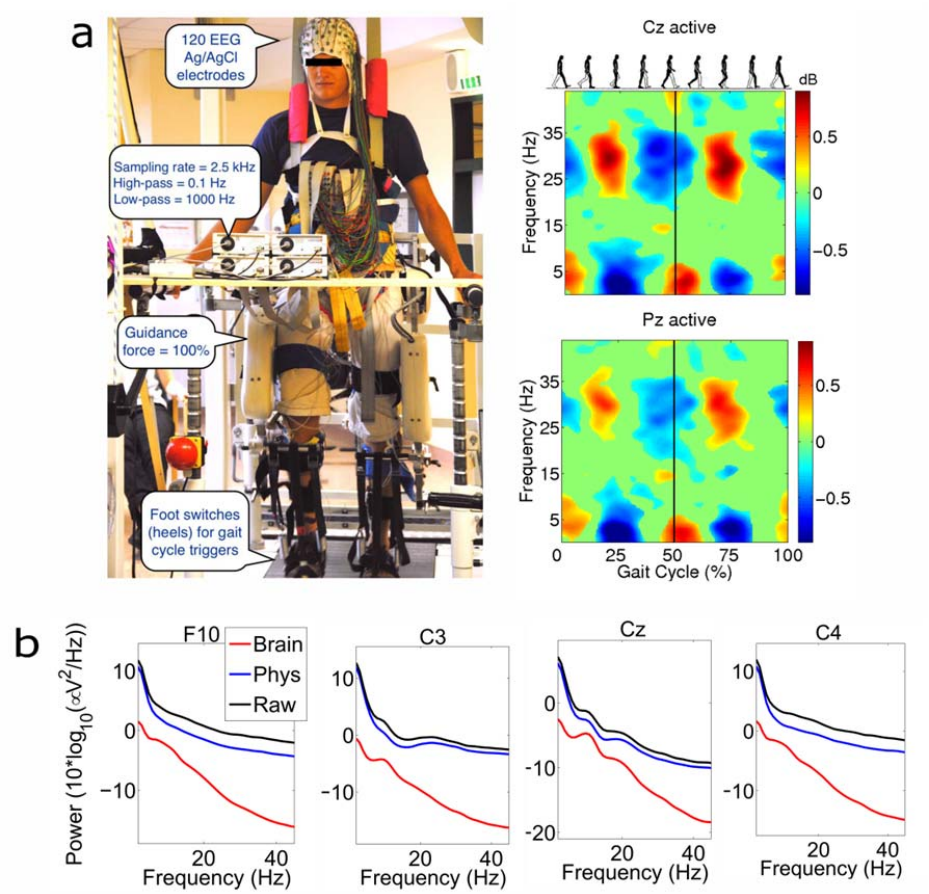

Fig. 4.1. Experimental setup; average EEG channel power spectral density (PSD) at electrodes F10, C3, Cz, C4 and P10 and average event related spectral perturbation (ERSP) plots for Cz and Pz. *(a) (From left to right) Experimental setup: subject walking in the Lokomat gait orthosis with body weight support. The amplifiers for EEG recordings are fixed on a board in front of the participant. The orthosis is adapted and fixed to the participant's legs with the help of an experienced physical therapist; average ERSP plots over all subjects for channels Cz and Pz showing significant changes in spectral power during the gait cycle for active walking. Non-significant differences relative to the full gait cycle baseline ($p \leq 0.05$) are masked in green (0 dB). The right leg heel contact marks the beginning and end of the gait cycle, the vertical line signs the temporally aligned event of left heel-strike (50%). (b) For three artifact rejection stages: 1. Channel based artifact removal (black line), 2. After removing non physiological artifacts (blue line) 3. Retaining only activity classified as cortical (red line), for channels F10, C3, Cz, C4 and P10. Panel a: (Part of this image was modified from http://atec.utdallas.edu/midori/Handouts/walkingGraphs.htm).*

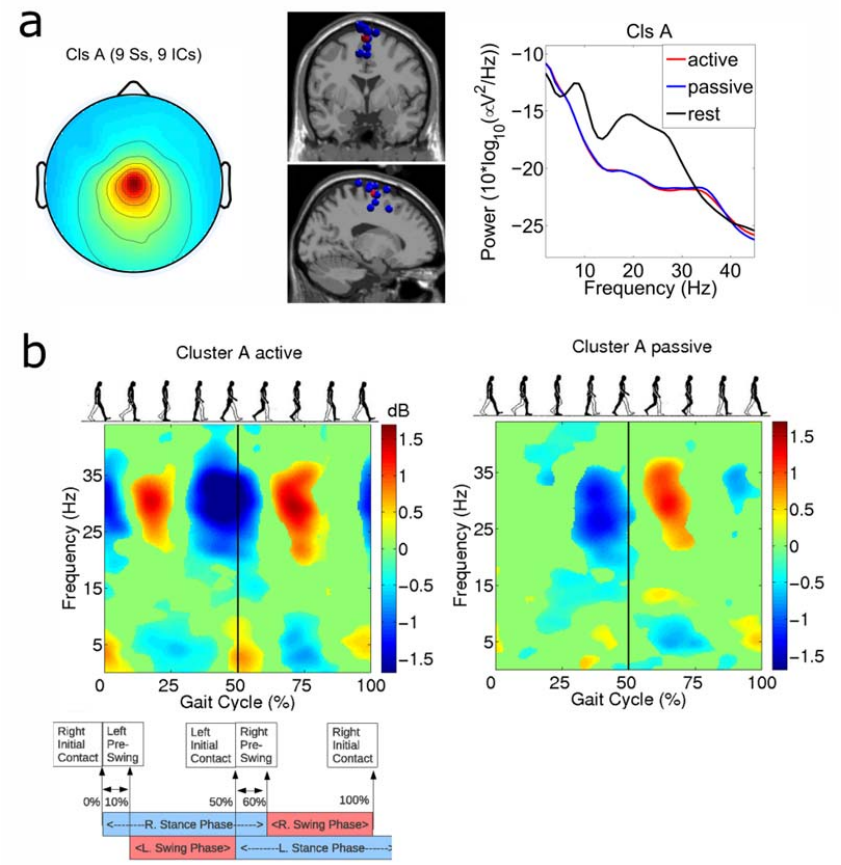

Fig. 4.2. Scalp projection, dipole locations, power spectral density (PSD) and Event related spectral perturbations (ERSPs) for cluster A, located in the premotor cortex. *(a) (From left to right) Cluster average scalp projection; dipole locations of cluster ICs (blue spheres) and cluster centroids (red spheres)visualized in the MNI brain volume in coronal and sagittal views; gait cycle PSD for active and passive walking and standing; (b) average cluster ERSP plots showing significant changes (relative to the full gait cycle baseline ($p \leq 0.05$)) in spectral power during the gait cycle for active walking (bottom left), and passive walking (bottom right). Non-significant differences are masked in green (0 dB). The right leg heel contact marks the beginning and end of the gait cycle, the vertical line signs the temporally aligned event of left heel-strike (50%). Part of this image was modified from http://atec.utdallas.edu/midori/Handouts/walkingGraphs.htm.*

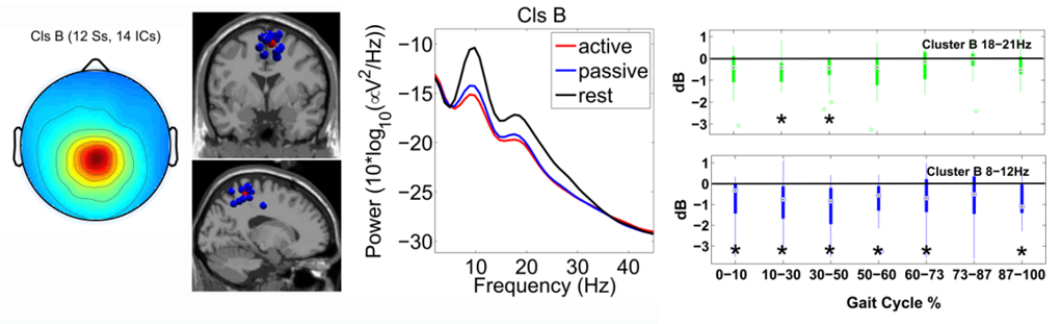

Fig. 4.3. Scalp projection, spatial location and power spectra of independent component cluster. B located in the sensorimotor cortex, foot area*; From left to right: Cluster average scalp projection; dipole locations of cluster ICs (blue spheres) and cluster centroid (red spheres) visualized in the MNI brain volume in coronal and sagittal views; PSD for active and passive walking and standing. A significant difference in PSD between active and passive walking and standing in the mu and in the beta range has been observed; boxplot showing differences (active minus passive walking) in normalized average spectral power for the single gait cycle phases. The edges of the box mark the 75th percentiles, black dots the median. Whiskers sign the range of values, outliers are plotted as empty circles. Significant differences are marked with * for p≤0.05 and ** for p≤0.01; these difference plots are displayed for Cluster B in the mu and beta bands.*

4.2. STUDY II: It's how you get there: walking down a virtual alley activates premotor and parietal areas

Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C., & Müller-Putz, G. (2014). *Frontiers in human neuroscience*, *8*. *doi: 10.3389/fnhum.2014.00093*

It has been proposed that post-stroke functional reorganization of the motor cortex can be guided by principles of motor learning (Nudo, 2003). A factor that has been shown to be crucial for the encoding of motor memory is voluntary drive in the movement (Lotze et al., 2003; Kaelin-Lang et al., 2005). Two distinct subjective experiences have been associated with voluntary movements: 'intention' which relates to the experience of being about to do something and 'agency' which refers to the feeling that our movements generate some effect in the environment (Tsakiris et al., 2010). Thus, the feeling of agency can be enhanced when our actions are accompanied by visual or sensory feedback (Blakemore et al., 2002). In line with these observations the execution of a functional task to reach some behavioral goal has been shown to be related to motor learning (Diamond et al., 1964, Greenough et al., 1985, Kleim et al., 1996, Rosenzweig et al., 1964, Plautz et al., 2000) and promote cortical changes related to post-stroke lower limb recovery (Adkins et al., 2006, Liepert et al., 2000, Van Peppen et al., 2004). In post-stroke locomotor rehabilitation Virtual Environments (VEs) in combination with robotic gait trainers provide the possibility to implement functional tasks and provide visual feedback relative to lower limb movements.

To determine whether walking in a Virtual Environment (VE) would generate motor planning and intention we examined the impact of an interactive VE feedback task on the EEG patterns during robot assisted gait training in able bodied participants. We compared walking in the VE to two control conditions: Walking with mirror feedback, in which participants observed their own movements and walking with a visual attention paradigm, in which visual stimuli were unrelated to the motor task. We hypothesized that interactive feedback in a VE would suppress mu and beta rhythms and thus activate premotor and parietal cortices - areas that have been previously related to motor planning and intention. Additionally, we hypothesized that if the VE task would yield higher cortical activation of these areas compared to mirror feedback interactive VE feedback may be more beneficial for motor learning.

Major contributions: The analysis showed that the interactive VE feedback task significantly suppresses mu and beta rhythms in premotor and parietal areas compared to mirror feedback and motor unrelated feedback. Such suppression indicates increased activation of these brain areas that have been related to motor planning. Interestingly the interactive feedback task induced a higher activation in the right parietal lobe, a brain area that has been related to the feeling of agency (Tsakiris et al., 2010). Furthermore this is the first study to show the involvement of a premotor-parietal network in visuomotor integration during walking. Activity in the parietal cortex likely reflects direct visuomotor transformations related to gait movements required by the task. We also show that low gamma power changes (25 to 40Hz) relative to gait cycle phases are modulated by motor planning during visually guided gait adaptation. The results of this study suggest that goal directed walking tasks recruit brain areas involved in motor planning and agency and may thus promote motor learning in post-stroke gait rehabilitation therapy.

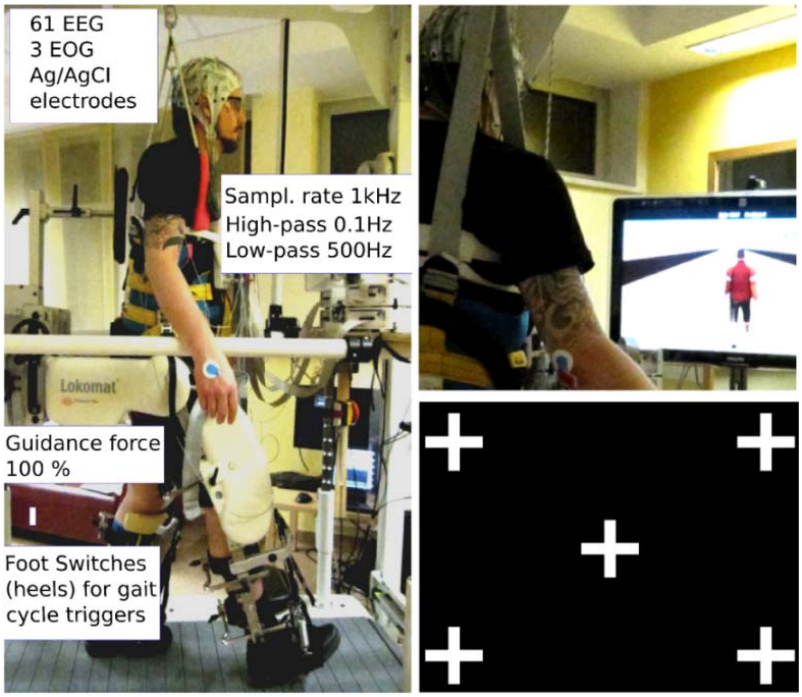

FIGURE 4.4. Experimental setup: subject walking in the lokomat gait orthosis with bodyweight support. *The amplifiers for EEG recordings are fixed on a board in front of the participant. The orthosis is adapted and fixed to the participant's legs with the help of an experienced physical therapist; Left: robotic assisted walking. Speed (≤2.2 km/h) and body weight support (~30%) were adjusted for each participant; Right top: participant walking in the virtual environment (VE) condition with 3rd person view. Right bottom: gaze screen with possible locations for the graphical objects. Participants were instructed to walk in the gait orthosis and focus their gaze on objects appearing on the screen*

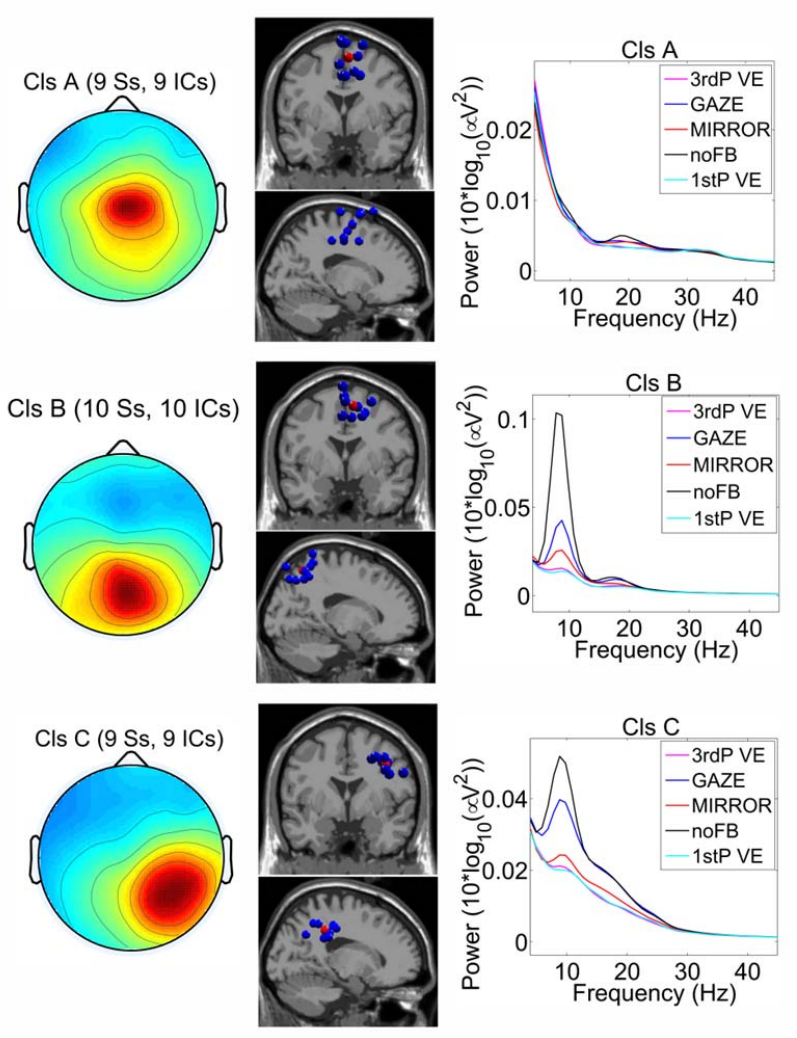

FIGURE 4.5. Scalp projection, spatial location and power spectra of independent component clusters (A) Cluster A located in the supplementary motor area(premotor cortex); (B) Cluster B located in the posterior cortex (Brodmannarea7); (C) Cluster C located in the posterior cortex (Brodmannarea 40). *From left to right in each row: cluster average scalp projections; dipole locations of cluster ICs (blue spheres) and cluster centroids (red spheres) visualized in the MNI brain volume in coronal and sagittal views; PSD for all feedback conditions. For cluster B and C a clear difference in PSD between noFB and Gaze vs. both of the VE conditions in the mu and in the beta range can be observed [Naming: Ss, ICs - number of subjects (Ss) and Independent Components (ICs) in the cluster].*

4.3. STUDY III: Distinct beta band oscillatory networks subserving motor and cognitive control during gait adaptation

Wagner, J., Makeig, S., Gola, M., Neuper, C., Müller-Putz, G.R. *submitted*

Everyday locomotion and obstacle avoidance requires effective gait adaptation. Many studies have shown that efficient motor actions are associated with mu rhythm (8 to 13 Hz) and beta band (13 to 35 Hz) power desynchronizations in sensorimotor and parietal cortex, while a number of cognitive task studies have reported higher behavioral accuracy to be associated with increases in beta band power and coherence in prefrontal and sensory cortex. How these two distinct patterns of beta band oscillations interplay during gait adaptation, however, has not been established. Here we recorded 108-channel electroencephalographic (EEG) activity from 18 participants attempting to walk on a treadmill in synchrony with a series of pacing cue tones while also adapting their step rate and length as quickly as possible to sudden shifts in the tempo of the pacing cues.

This paper has been submitted to a scientific journal but has not yet been published at the time of writing the thesis. Therefore the submitted manuscript is included in this section.

Major contributions: Understanding brain dynamics supporting gait adaptation is crucial for understanding motor problems in walking such as those associated with stroke and Parkinson's and could guide development of rehabilitative therapies for these conditions. Only a few electromagnetic brain imaging studies have examined neural correlates of human upright walking. Here, application of independent component analysis to EEG data recorded during treadmill walking allowed us to uncover two distinct beta band oscillatory cortical networks that are active during gait adaptation: (8 to 13 Hz) mu rhythm and (13 to 35 Hz) beta band power decreases in central and parietal cortex and (14 to 20 Hz) beta band power increases in frontal brain areas. In the right dorsolateral prefrontal cortex (dlPFC), the beta band power increase was stronger during (more effortful) step shortening than during step lengthening, possibly related to inhibitory motor control. These results show that two distinct patterns of beta band activity modulation accompany gait adaptations, one likely serving movement initiation and execution and the other, motor control and inhibition.

4.3.1. Introduction

Impairment in gait adaptability (i.e., one's ability to change walking speed or direction as required) (Den Otter et al., 2005, Hofstad et al., 2006) produces a reduced ability to avoid obstacles and an increased risk of falling in affected individuals including many stroke and Parkinson's patients (Weerdesteyn et al., 2006). Rhythmic auditory cues have been widely used in the rehabilitation of gait (Thaut & Abiru, 2010). Use of an auditory pacing stimulus stream including infrequent tempo shifts has been recommended to identify deficits and train improvements in gait adaptation in stroke patients (Roerdink et al., 2009, 2007). Unfortunately, because of the ill effects of movements on brain imaging data the precise temporal brain dynamics of step adaptation remain largely unexplored in neuroimaging studies. Recent signal processing advances, however, allow study of source-resolved EEG dynamics

during walking (Gwin et al., 2010, 2011, Gramann et al., 2011, Seeber et al., 2015) and other actions, an approach termed Mobile Brain/Body Imaging (MoBI) by Makeig and colleagues (2009).

Previously we have reported mu-rhythm and beta-band power decreases (desynchronizations) over central sensorimotor and parietal areas during active walking relative to standing or passive walking (i.e., when participants' legs are moved by a robot) (Wagner et al., 2012, Seeber et al., 2014a) and during step adaptation to interactive visual feedback in a virtual environment (Wagner et al., 2014a). Mu and beta band power in the motor system decrease during the preparation and voluntary execution of movements (Jasper & Penfield, 1949, Pfurtscheller & Berghold, 1989, Pfurtscheller & da Silva, 1999) while beta band power increase in scalp EEG data has been related to movement suppression (Gilbertson et al., 2005, Androulidakis et al., 2007, Zang et al., 2008, Pogosyan et al., 2009, Joundi et al., 2012, Solis-Escalante et al., 2012).

Electrophysiological studies suggest that beta band oscillations may also index top-down signaling. For example, visual top-down attention and behavioral rule switching are related to oscillatory synchronization of beta-band local field potentials in monkeys' prefrontal cortex (PFC) and parietal cortex (Buschman et al., 2007; 2012). PFC effects top-down control by sending information about goals and appropriate actions to other brain areas (Miller & Cohen, 2001). Swann and colleagues (2009) reported that an electrocortical beta band power increase in PFC during motor inhibition preceded mu and beta band power decreases in motor cortex, while in older subjects beta band activity increases may have compensatory effects (Geerligs et al., 2012, Gola et al., 2012; 2013).

Recent studies of gait adaptation using EEG showed increased event-related potential (Haefeli et al., 2011) and hemodynamic responses (Suzuki et al., 2004) during preparation for and performance of stepping over obstacles, as well as during adaptive walking and precision stepping (Koenraadt et al., 2013). A recent study demonstrated that during gait adaptation stroke patients prefer step lengthening over step shortening (Roerdink, 2009), suggesting that brain mechanisms controlling voluntary gait acceleration and deceleration differ (Varraine et al., 2000). Recent studies have reported that performing a secondary task during walking induces participants to take longer strides (Li et al., 2012, Lovden et al., 2008, De Sanctis et al., 2014), suggesting that step lengthening requires fewer attentional resources.

To examine whether difficulty in gait adaptation is related to PFC beta band activity, we designed a high-density EEG study in which participants walking on a treadmill moving at a steady rate had to adapt their step length and rate to shifts in the tempo of a pacing tone (i.e., shifts requiring both longer and shorter step responses). We expected three different processes would accompany step rate adaptations to auditory tempo shifts: 1) mu and beta band desynchronization in sensorimotor and parietal cortex, reflecting increased motor flexibility and adaptation; 2) increased beta band power within the PFC, reflecting additional cognitive control; 3) scaling of PCF beta band power changes with task difficulty, producing a stronger increase in beta band power during step shortening than during step lengthening.

4.3.2. Materials and methods

Participants. Twenty healthy volunteers with no neurological or motor deficits participated in this study. The data of two subjects were excluded because of heavy EEG artifact. The remaining data of eighteen subjects (ten males and eight females aged 22 to 35 years; mean, 29.1, std. dev., 2.7) was considered in the analysis. All participants were right handed. Prior studies show that footedness follows handedness in right handers, though not consistently so in left handers (Peters & Durding, 1979). The experimental procedures were approved by the human use committee of the Medical University Graz. Each subject gave informed consent before the experiment.

Experimental design and procedure. Figures 4.6 and 4.7 show the experimental setup and a schematic of the task paradigm, which was adapted from Bank et al. (2011).

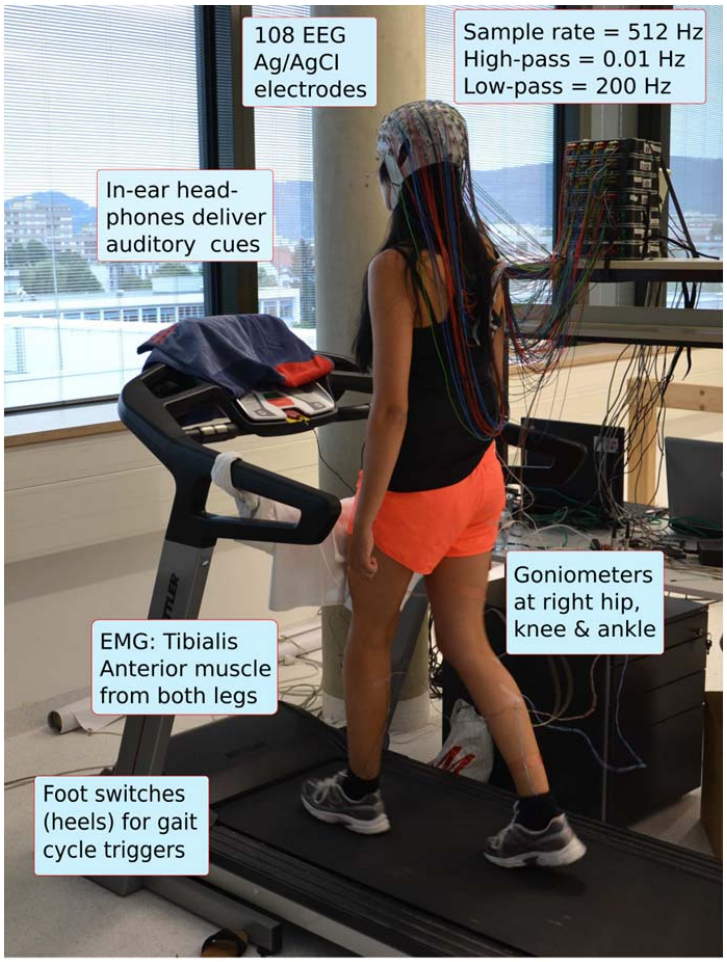

Figure 4.6. Experimental setup: *Participant walking on the treadmill with auditory pacing cues delivered through in-ear headphones. During the initial training period, treadmill speed (3-3.5 km/h) was adjusted to the most comfortable pace for each participant and thereafter remained constant.*

Training. Prior to the experimental procedure participants practiced walking on the treadmill for 2-3 minutes. While walking on the treadmill participants adapted the belt speed to their most comfortable

walking speed; this ranged from 3.0 to 3.7 km/h across participants. Belt speed was then fixed at the participant's comfortable walking speed and thereafter remained constant throughout the experiment. Next, participants practiced the gait adaptation task with auditory pacing to become familiar with the task and to reach acceptable performance, meaning that they correctly responded to step-advance and step-delay pacing signal tempo shifts by shortening or lengthening their steps correspondingly so as to synchronize their steps to the new tempo.

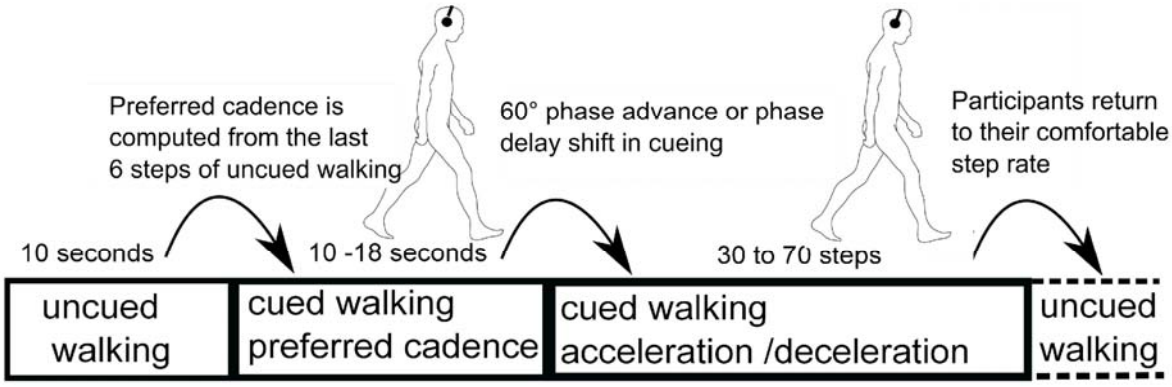

Figure 4.7. Experimental paradigm: *Throughout the session, treadmill speed remained fixed at a rate comfortable to the participant. During each roughly minute-long trial, participants first walked for about 10 sec without auditory cues, then walked for 10-18 sec synchronous with cue tones delivered at their then-prevailing step rate and phase. Thereafter, beginning at a right heel strike, a sudden (accelerated or decelerated) tempo shift occurred in the pacing cue sequence. In response, participants were instructed to adapt their step length, rate, and phase as quickly as possible so as to again synchronize their steps with the cue tones at the new tempo. After 30 to 70 steps at the new step rate, the next trial began immediately, returning again to 10 sec of uncued walking during which participants were instructed to return to their most comfortable step rate.*

Trial structure. During each roughly minute-long trial period participants first walked without pacing cues for about 10 seconds. During the next 8 to 12 seconds, they heard a stream of auditory cue tones delivered via in-ear headphones at a tempo matching to their current step tempo (the mean of the step intervals between their six most recent six uncued steps). The cue sequence was an alternating series of high and low tones presented so as to match the participant's right and left (or left and right) heel strikes respectively (this high/low assignment was randomized over subjects). Participants were asked to synchronize their heel strikes to the cue tones.

Next, following a randomly selected right heel strike (after 8 to 12 s of cued walking) the tempo of the cue sequence was suddenly increased or decreased by $1/6^{th}$ of a cycle (60 deg) (as in Roerdink *et al.,* 2009) and this new cue tempo was maintained for 30 to 70 steps. Participants were instructed to adjust their heel strikes so as to synchronize with the new cue sequence as quickly as possible. The gait adjustments required to restore synchronization with the metronome were: a $1/6^{th}$ longer step interval and step length in (+60° phase shift) step-delay trials, and a $1/6^{th}$ shorter step interval and step length in (-60° phase shift) step-advance trials. After 30 to 70 steps at the new step rate, the next trial began immediately with, again, uncued walking, during which participants were instructed to return to their most comfortable step rate.

A total of 60 step-advance and 60 step-delay trials were conducted in 10 blocks of 12 trials each comprised of 6 step-advance and 6 step-delay trials presented in random order. Between blocks, when asked for by participants short breaks of 5 minutes were given during which participants were standing on the treadmill.

Data acquisition. Seven 16-channel amplifiers (Gtech, Graz, Austria) were combined so as to record EEG data from 108 electrode channels in the 5% International 10/20 System (EasyCap, Germany) (Oostenveld & Praamstra, 2001). Electrode locations that extended below the conventional 10–20 spherical layout included PO9, POO9, OI1, OI2, POO10, PO10, I1, Iz, and I2. Reference and ground electrodes were placed on the left and right mastoids respectively. All electrode impedances were reduced to below 5 kΩ before the recording. Electromyographic (EMG) signals were recorded from the skin over the tibialis anterior muscles of both legs using standard adhesive-fixed disposable Ag/AgCl surface electrodes. These EMG channels were also recorded using left and right mastoids as reference and ground respectively. The EEG and EMG data were sampled at 512 Hz, high pass filtered above 0.1 Hz, and low pass filtered below 256 Hz. Foot contacts were measured by mechanical foot switches placed over the calcaneus bone in the heel of each foot. These switches produced event markers for gait cycle heel strike and heel off events. To record the exact timing of the auditory cues we recorded the auditory stimulation via digital inputs to one of the amplifiers.

Behavioral analysis. Two participant timing error correction processes have been distinguished: 1) period correction to bring the motor acts (here, heel strikes) to the same tempo as the stimulus sequence (Michon, 1967), and 2) phase correction to make the motor acts coincident with pacing stimulus onsets by compensating for any phase difference (Repp, 2001a, 2001b). To assess sensorimotor synchronization we thus analyzed phase correction and period correction separately. Phase correction was assessed by computing asynchronies between heel strikes and pacing tone onsets (for an overview, see Repp, 2005, Repp & Su, 2013) while period correction was assessed by computing temporal differences between cue intervals (time intervals between consecutive cue onsets) and step intervals (or step onset asynchronies, intervals between consecutive heel strikes).

Phase correction. For each trial, the relative phase angle difference between each heel onset and the corresponding auditory cue was calculated. Phase was defined as $phase = 360° * (tcue - tHS)/Tcue$, with *tcue* (in ms) denoting the time of cue onset, *tHS* denoting the time of the nearest heel strike, and *Tcue* denoting the time interval between consecutive ipsilateral step cues (Roerdink *et al.,* 2007). For each trial, pre-shift coordination between steps and cues was quantified by computing the mean and standard deviation phase angle difference in the five steps immediately preceding the tempo shift. The time course of gait adjustments made by the participant to restore coordination following cue tempo shifts was quantified by calculating the phase difference from baseline for the 14 steps following the shift and dividing by ±60 so that *step phase* at S0 (the first time-perturbed stimulus) was +60° (Pelton et al., 2010, Roerdink et al., 2009). Trials were excluded from analysis if any of the steps exceeded normalized phase of 180° which corresponds to a 180° difference from pre-manipulation performance. Based on these criteria, on average 5 (std. dev., ±6) shift trials were excluded (6% of all trials).

A 2×14 repeated measures ANOVA with factors “tempo shift” (long vs. short) and “step number” (step numbers 1 to 14 following the shift) was used to assess significant differences in fidelity

of adaptation. between step-advance and step-delay shifts. *Post hoc* tests were corrected *a priori* to a significance level of 0.05 using false discovery rate (Benjamini & Yekutieli, 2001).

EEG analysis. EEG data analysis was performed using custom scripts written in Matlab 2014a (The MathWorks Inc., Natick, MA) incorporating EEGLAB 14.0b functions (Delorme & Makeig, 2004). In Wagner et al. (2012, 2014a) we showed that artifact contamination of the EEG during upright walking can be separated from the brain source data using Infomax Independent Component Analysis (cf. Onton et al., 2006, Gwin et al., 2010).

The EEG data were high-pass filtered at 1 Hz [zero phase FIR filter, order 7,500] to minimize slow drifts, and low pass filtered below 200 Hz [zero phase FIR filter, order 36]. EEG channels with prominent artifacts were identified by visual inspection and removed. On average, 106 channels (std. dev. 2.2; range: 102 to 108) per participant remained for analysis. The EEG data were then re-referenced to a common average reference. After visually rejecting artifacts in the continuous EEG, the data were partitioned into epochs of 0.5 s and segments with values exceeding the average of the probability distribution of values across the data segments by ±5 SD were rejected. On average, an average of 45 post-shift steps per condition (80% of each participant's EEG data) remained in the analysis (range, 71% to 89%; std. dev., ±11%).

Next, the preprocessed EEG data were decomposed using adaptive mixture independent component analysis (AMICA) (Palmer et al., 2006; 2008). AMICA is a generalization of the Infomax ICA (Bell & Sejnowski, 1995, Makeig et al., 1996) and multiple-mixture (Lee et al., 1999, Lewicki & Sejnowski, 2000) ICA approaches. AMICA performed blind source separation of all concatenated preprocessed data trials for each individual subject individually, based on the assumed temporal near-independence of the effective EEG sources (Makeig *et al.,* 2002, 2004).

Using a standardized three-shell boundary element head model (BEM) implemented in the DIPFIT toolbox within EEGLAB (sccn.ucsd.edu/eeglab) we calculated a best-fitting single equivalent current dipole matched to the scalp projection of each independent component (IC) source (Delorme et al., 2012, Oostenveld & Oostendorp, 2002). Standard electrode locations corresponding to the Extended 10-20 System were aligned with a standard brain model (Montreal Neurological Institute, MNI, Quebec, Canada). We retained ICs for further analysis for which the equivalent dipole model a) explained more than 90% of variance of the IC scalp map and b) was located within the brain.

We visually inspected the remaining IC scalp maps, event-locked time courses, and mean power spectra to identify ICs related to non-brain source artifacts (eye movement and scalp/neck muscle artifacts). Non-artifactual ICs were retained for further analysis. For these, feature vectors were constructed coding IC differences in dipole locations, scalp projection maps, and power spectral densities (PSD) (3 to 45 Hz) (Makeig et al., 2002). Using principal component analysis (PCA) these feature vectors were reduced to 10 principal components and clustered using k-means (k = 18). ICs were identified as outliers if their locations in the clustering vector space were more than five standard deviations from the obtained cluster centers. Only clusters including ICs from more than half of the participants are reported here.

Cortical IC Clusters. The data were segmented into time epochs relative to onsets of cue tempo shifts (e.g., from -4 s to 10 s around the first right post-shift heel strike). Event-related spectral perturbations

(ERSP) (Makeig, 1993) were computed for each IC. Single-trial spectograms were computed and time warped to the median step latency (across subjects) using linear interpolation. This procedure aligned time points of right and left heel strikes over trials for the 7 heel strikes preceding and the 15 heel strikes following each tempo shift. Relative changes in spectral power were obtained by computing the mean difference between each single-trial log spectogram and the mean baseline spectrum (the average log spectrum between -4 s to -0.5 s preceding tempo shifts). Significant deviations from the baseline were detected using a non-parametric bootstrap method (Delorme & Makeig, 2004).

To compute significant differences between step-advance and step-delay shifts, individual frequency bands were selected per subject by determining ranges from 8 to 13 Hz (alpha) 14 to 20 Hz (lower beta), 21 to 35 Hz (upper beta), and choosing the frequency band with maximally varying power modulation over time. For statistical analysis, ERSPs relative to step-advance and step-delay shifts were computed by time warping single trial spectrograms to the same (group median) step latencies and subtracting the overall average log spectrum for both conditions computed from -4 s to -0.5 s before the tempo shift. For statistical analysis, we selected four time windows centered on the first left (L1) and second right (R2) steps following tempo shifts.

A 2×4 repeated measures within-subject ANOVA with factors "tempo shift" (long vs. short) and "step number" (4 time windows) was computed for each IC cluster and each frequency range (alpha, lower beta, upper beta) in the (individually subject-selected) dominant frequency range. Multiple comparisons were corrected by controlling for false discovery rate (Benjamini and Yekutieli, 2001) with an *a priori* significance level of $p = 0.05$. In cases in which the assumption of sphericity was violated, significance values were Greenhouse-Geisser corrected.

4.3.3. Results

Behavioral Analysis. Step onset asynchrony (StOA) before tempo shifts was on average 641 ms (std. dev., ±5.3 ms). Following tempo shifts a new stable StOA was generally achieved within 3±1 steps, as shown in Figure 4.8C. Step-delay shifts (+60°) produced increases in both StOA (754 ms (calculated for the first 15 steps following shifts); std. dev., ±14 ms) and step length, while step-advance shift (-60°) produced decreases in StOA (mean time between steps, 523 ms; std. dev., ±13 ms) and step length. These changes were fairly large, on average 18% relative to baseline, slightly larger than the expected $1/6^{th}$ (16.7%), though not significantly so.

Period correction. The evolution of adjustments in step rate to the two new pacing frequencies for all participants are depicted in Figure 4.8D which also shows the difference between StOA and cue onset asynchrony (COA). On average, period adaptation was achieved well within the first two steps (between L1 and R2). During the four steps following, an overcorrection (R2) occurred, after which participants seem to match perfectly the new pacing frequency.

Phase correction. Negative StOA - COA differences indicate that the step onset preceded stimulus onset. As shown by comparing the step latency histograms in Figure 4.8B with the median step latencies in Figure 4.8C, during walking at the preferred cadence (e.g., steps -7 to -1 before the shift) we observed that heel strikes were consistently ahead of the cues (mean difference, -59 ms; std. dev.,

±43 ms). This difference matches a well-known phenomenon called 'phase lead' in finger tap synchronization studies. It has been suggested that this difference approximates the difference between the times of delivery of the sensory information from the tip of the finger and the auditory information from cue onset to the cortical areas in which their timing is compared. Thus, to establish synchrony at the level of central representations finger taps should precede the auditory signals (Aschersleben & Prinz, 1995; 1997) Adjustment of steps relative to cues was achieved within 6 steps following tempo shifts. As shown in Figure 4.8E, the phase lead between steps and cues (measured from steps 7 to 15 following the shift) became larger in step-delay (step lengthening) trials (mean, -122 ms; std. dev., ±61 ms), and became positive phase delay in step-advance (step shortening) trials (mean, 19 ms,; std. dev., ±36 ms).

Calculation of the normalized relative phase revealed differences in adaptation relative to positive and negative step rate changes. The direction of the tempo shift significantly affected synchronization accuracy (significant interaction, $F(13, 221) = 5.2$, $p = 0.00025$). *Post hoc* tests revealed a significantly larger initial phase deviation at steps L1 and R2 in step-advance compared to step-delay trials. Also, as shown in Figure 3F when participants reached stable post-shift cue synchronization, asynchrony between steps and cues was significantly larger in step-advance than in step-delay trials. This suggests that participants had fewer difficulties in adapting to step-delay compared to step-advance shifts.

Cortical IC source clusters. Altogether, three IC source clusters in frontal brain, one in left temporal cortex, one in central midline cortex, and two clusters in parietal areas showed event-related changes in alpha and beta band power following cue tempo shifts. The numbers of subjects and sources contained in each cluster as well as Tailarach coordinates of the cluster centroids are given in Table 4.1. Figure panels 4.8A and 4.8B show cluster location and average cluster spectral changes in right frontal cortex time locked to step-advance shifts. Comparing spectral changes (Figure 4.8B) and behavioral data (Figure 4.8C-F) shows that a right frontal beta band increase coincides with the main adaptation period of steps 2 to 4 after the shift. While, as shown in Figures 4.8B, 4.9 and 4.10, during the first four steps after the shift frontal and temporal clusters exhibited significant transient increases in alpha and/or beta power (13 to 20 Hz in frontal clusters, 7 to 20 Hz in the left temporal cluster), mu and beta band power in central midline and parietal clusters decreased during this time period (Figures 4.11 and 4.12). Interestingly, for the left and right parietal clusters (Figure 4.12) this desynchronization lasted at least 15 steps following tempo shifts, and was most pronounced just prior to contralateral heel strikes. The parietal cluster desynchronization was prominent and long lasting in two frequency bands: mu (7 to 12 Hz) and high beta (18 to 30 Hz).

In central medial sources (Figure 4.11), however, the desynchronization was not as strong but included higher frequencies (up to 35 Hz) and began immediately after the tempo shifts. Only the right frontal cluster showed a significant ERSP difference between step-delay and step-advance trials; this was in the lower beta band (14-20 Hz) ($F(1,18) = 9.67$, $p = 0.006$). This significant difference is highlighted in Figure 8 showing median beta band ERSPs and confidence intervals for step-advance and step-delay shifts in each frontal cluster. The difference-ERSP map for the r-dlPFC cluster (Figure 4.10) also showed a significantly larger increase in beta band power for step-advance compared to step-delay trials during the first left and second right steps following tempo shifts.

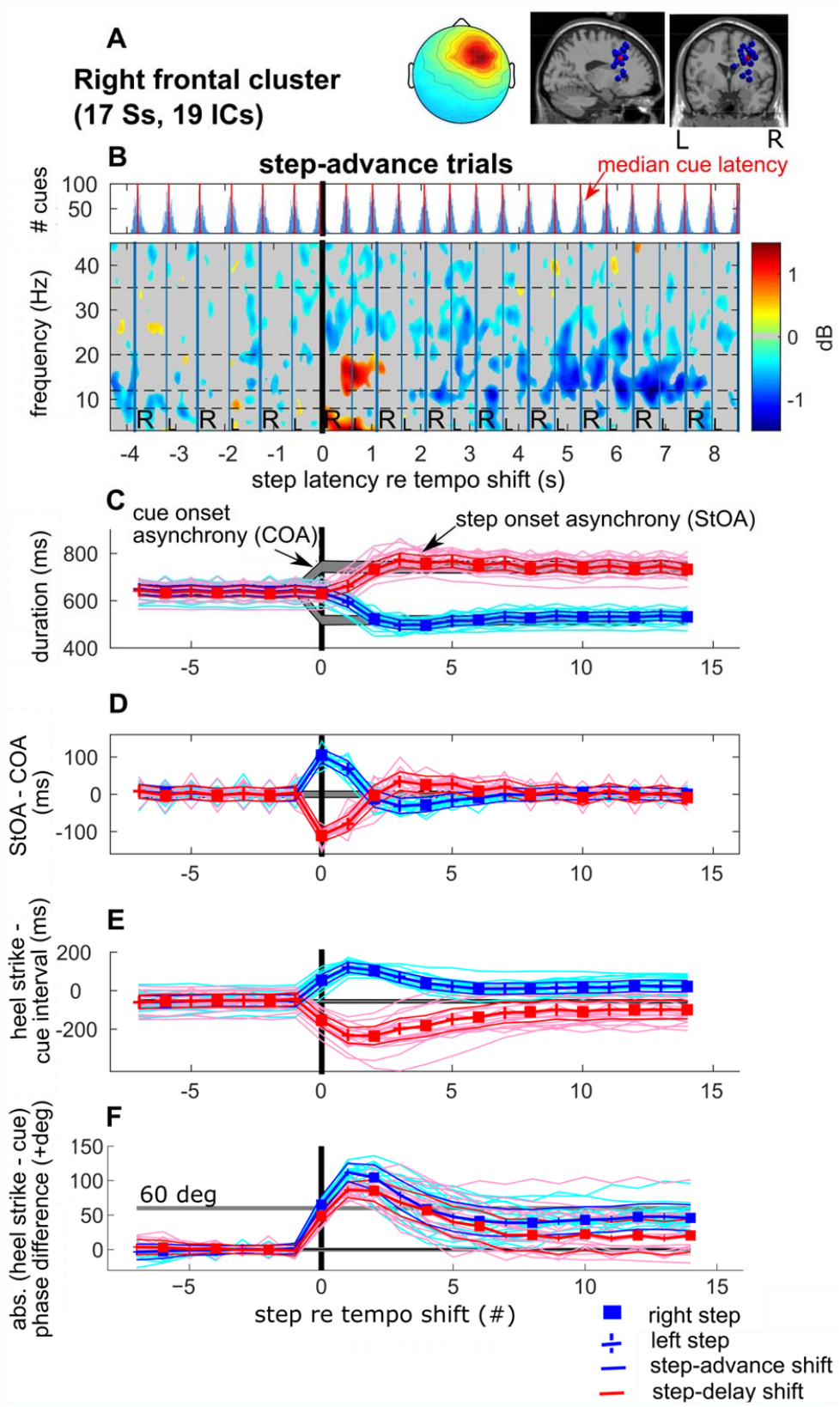

Figure 4.8. Event-related spectral perturbation (ERSP) and behavioral adaptation performance following tempo shifts. (A) *Cluster mean scalp projection map and equivalent dipole locations of cluster ICs (blue*

spheres) and their centroid (red sphere) visualized in the MNI template brain and located in and near right dorsolateral prefrontal cortex (r-dlPFC). ***(B)*** *Cue latency histograms (above) and cluster mean ERSP image (below) for the r-dlPFC IC source cluster in step-advance (step shortening) trials. Single-trial spectrograms were computed between -4 s to 10 s around the first time-shifted cue (0 s marks the target right heel strike). To construct the group-mean ERSP, for each subject the single-trial EEG spectrograms were first time warped to the group-median latencies of the heel strikes during the imaged interval (red vertical lines in the cue latency histograms). Relative changes in spectral power were obtained by subtracting the mean log spectrum in the interval -4 s to -0.5 s before the shifts. Non-significant changes from baseline are masked in grey. Vertical lines mark right and left heel strikes; R's and L's mark right and left foot placements. Dashed horizontal lines mark alpha (8 to 13 Hz) lower beta (13 to 20 Hz) and upper beta (20 to 35 Hz) bands. The ERSP plot shows, first, a synchronization in the beta band between the second and third heel strikes following the tempo shift, the later a desynchronization with respect to baseline.* ***(C)*** *Behavioral record: Median step onset asynchronies (StOA) (blue and red traces) for each subject in the two conditions (step advance and delay), and cue onset asynchronies (COA) (grey traces) in ms.* ***(D)*** *Difference between StOA and COA at each step; this reflects adaptation of step frequency to the pertrubed pacing cue tempo.* ***(E)*** *Time intervals (in ms) between heel strikes and nearest cue onsets reflect sensorimotor synchronization performance – e.g., step adaptation to the tempo-shifted cue sequence.* ***(F)*** *Absolute step-cue phase difference (in deg of the baseline cue cycle).*

Table 4.1. Independent component clusters and cluster centroid locations

Cluster	**Number of subjects (Ss) and sources (ICs)**	**Tailarach Coordinates**	**Brodmann Area**	**Cortical Location**
left temporal	13 Ss, 14 ICs	-42, -10, -5	BA21	Temporal lobe
frontal central	15 Ss, 15ICs	-1, 39, 31	BA9	Medial Prefrontal Cortex
left frontal	13 Ss, 15 ICs	-28, 20, 25	BA9	Dorsolateral Prefrontal Cortex
right frontal	17 Ss, 19 ICs	28, 20, 29	BA9	Dorsolateral Prefrontal Cortex
central midline	11 Ss, 11 ICs	3, -2, 47	BA6	Supplementary Motor area
left parietal	13 Ss, 16 ICs	-34 ,-29, 42	BA40	Parietal Cortex
right parietal	14 Ss, 16 ICs	35, -44, 37	BA39	Parietal Cortex

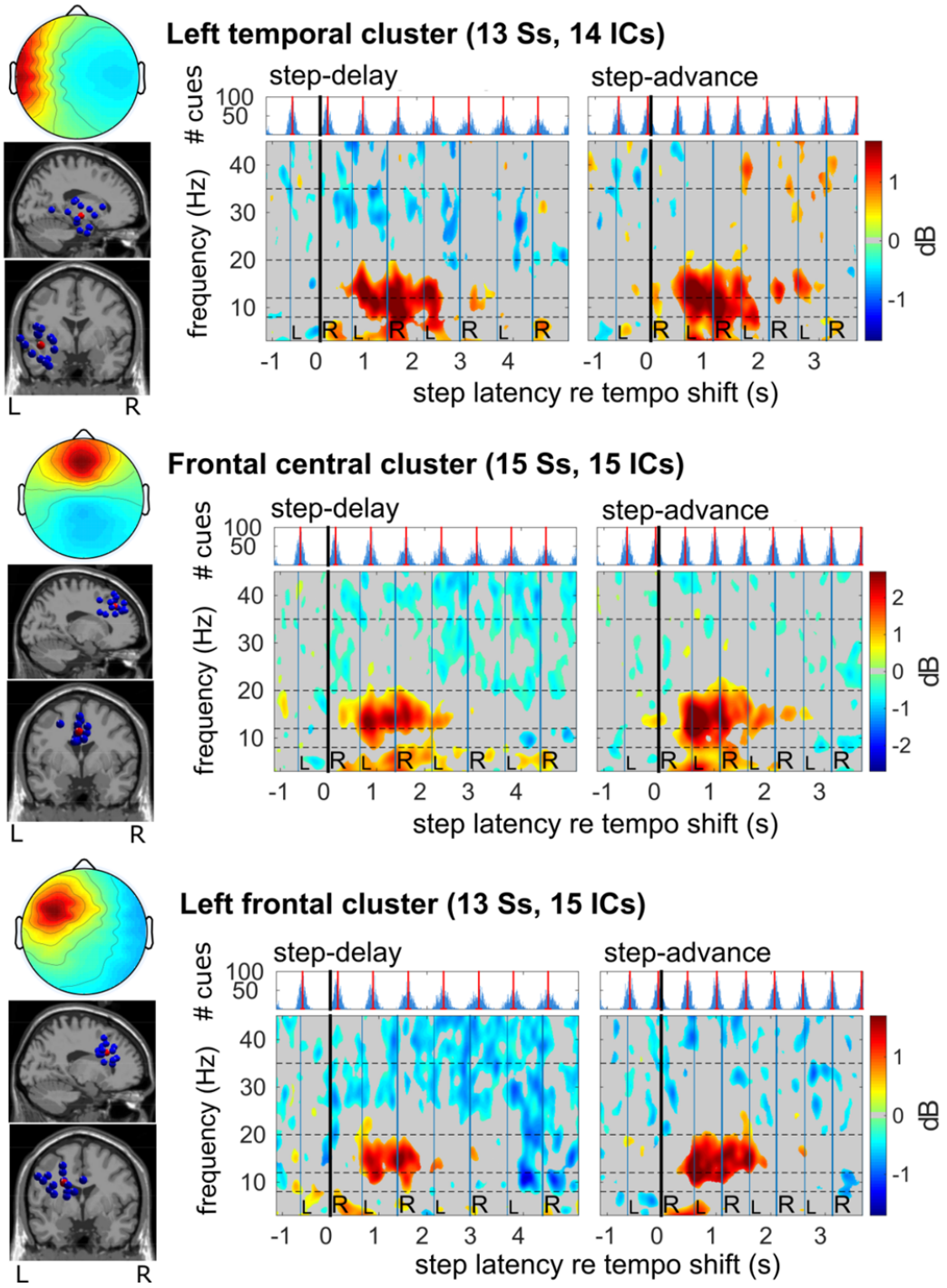

Figure 4.9. Scalp projection, spatial location and cluster mean ERSP images for IC source clusters located in temporal and frontal cortex. *From left to right in each row: Average scalp projection, and dipole locations of cluster ICs; cue onset histogram and cluster mean ERSP images time locked to (left) step lengthening (step delay) and (right) shortening (step advance) tempo shifts beginning with the cue nearest to the right heel strike (0 s). Single-trial log spectrograms were time warped to median step latencies before averaging. Mean log power at each frequency from -4 s to -0.5 s before the tempo shift was subtracted to obtain relative changes in log spectral power. Non-significant changes from baseline are masked in grey. All three IC clusters show increases in mean beta band power between the second and fourth heel strikes following the shift.*

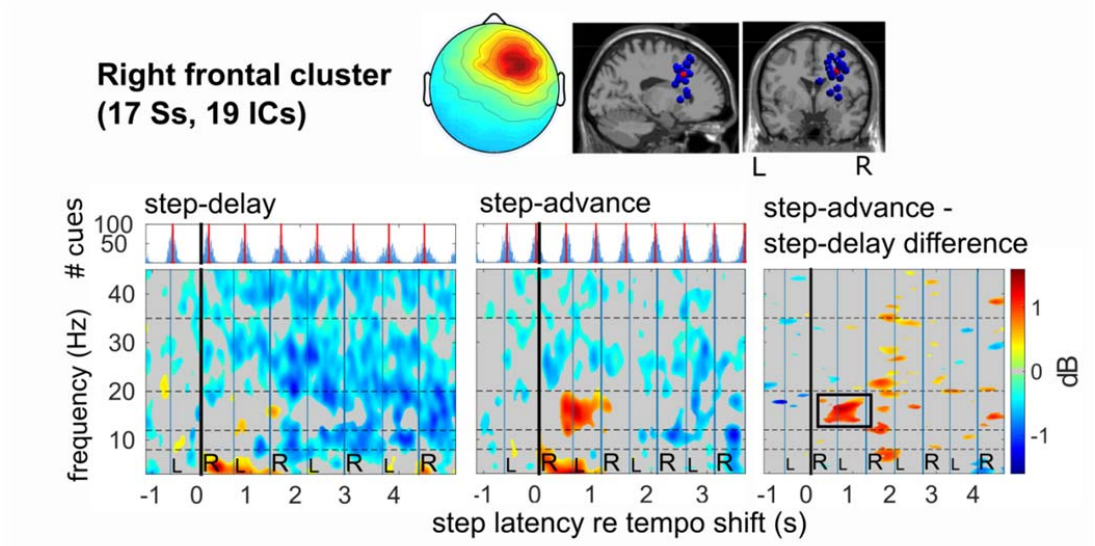

Figure 4.10. Significant event related spectral differences between adaptations to step-advance and step-delay tempo shifts in and near right dorsolateral frontal cortex. *Top: Average scalp projection and equivalent dipole locations of cluster ICs. Bottom: (above) Cue tone onset histograms and (below left, center) source cluster mean ERSP images for step-delay and step-advance trials respectively, time locked (0 s) to the nearest right heel strike to the first tempo-shifted cue tone, and (right) the difference between these two adaptation responses. Significance of condition differences were computed using a bootstrap method and corrected for multiple comparisons using false discovery rate. Non-significant differences are masked in grey. The difference ERSP shows stronger beta band power increase near the second and third post-shift steps in step-advance than in (subjectively easier) step-delay shift adaptations.*

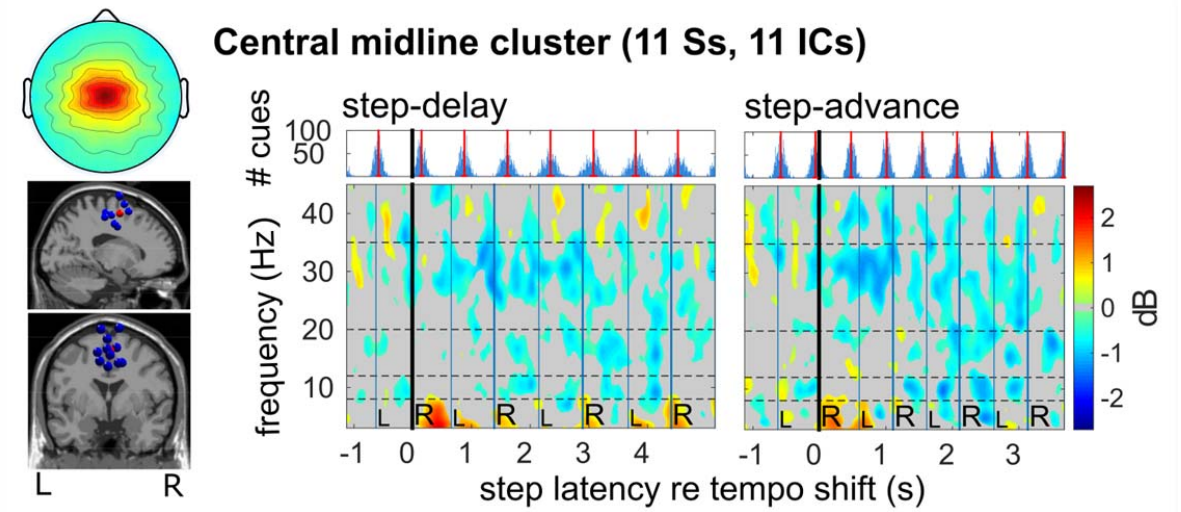

Figure 4.11. Mean scalp projection, brain locations, and cluster mean ERSP images for the IC source cluster located in and near supplementary motor area (SMA). *Cluster mean ERSP images relative to step lengthening and step shortening tempo shifts include desynchronization in the upper beta band (25 to 35 Hz). Other details as in Figure 4.*

4.3.4. Discussion

Use of a novel sensorimotor gait synchronization task, coupled with advanced EEG source signal processing methods, revealed two different beta band oscillatory networks involved in orchestrating motor adjustments during gait adaptation. Our results thus combine, mu and beta band power desynchronization (blocking) in motor and parietal cortex (PPC), with a concurrent beta band power increase in PFC. This indicates two distinct patterns of beta band activity during gait control:

1) a motor cortical mu and beta band decrease expressing motor execution and motor readiness related to gait movements (as in Pfurtscheller & Da Silva, 1999, Neuper et al., 2006, Wagner et al., 2012; 2014a, Seeber et al., 2014a), and
2) a frontal beta band increase related to cognitive top-down control (as in Bushman et al., 2012, Swann et al., 2009).

Observed mu (7 to 13 Hz) and beta band desynchronization (13 to 30 Hz) (Figures 4.11 and 4.12) in the motor system after a shift in tempo of the pacing cue sequence may reflect an increased disposition for motor adjustments, as suggested by Engel and Fries (2010), possibly guided by the PFC as proposed by Miller and Cohen (2001, Siegel et al, 2012). The fact that we observed temporary increase in a frontal beta band oscillatory network (13 to 20 Hz; Figures 4.9, 4.10, and 4.13) during step tempo adaptation may reflect action monitoring and top down signaling from the PFC to the motor cortex. Our results also show that beta band power in right dlPFC was modulated by task difficulty. This lateralized frontal beta band power increase during step shortening may represent neurocognitive response inhibition processes that involve beta band rhythms.

Frontal beta band oscillations in motor control. Near the second and third heel strikes following shift onsets (Figures 4.9, 4.10 and 4.13), we observed an increase in beta band power in EEG sources localized to left, central, and right frontal cortex (Table 4.1). As proposed by Miller and Cohen (2001), these regions may play an important role in the top-down signaling of current behavioral goals to guide adjustment of motor plans. In our task the participant's goal was to adapt their gait to cue-induced shifts in step tempo, either a phase advance (more difficult) or a phase delay (easier). Comparison between decelerations and accelerations revealed significantly higher beta power in the right dlPFC during step-advance trials (Figures 4.10 and 4.13). This result is in line with our hypothesis and the study by Swann and colleagues (2009) showing a relationship between a beta band power (~16 Hz) increase in the right inferior frontal gyrus and successful response inhibition in a stop signal task. Since in our task step shortening (in step-advance trials) required inhibiting execution of the accustomed full stride action, it is probable that this process requires more explicit motor inhibition than step lengthening.

In fact our behavioral results show that participants performed significantly more accurate step delays (lengthening) than step advances (shortening), stepping closer in time to the step-delay cues. This is in line with finger tapping studies showing that motor adaptation is somewhat faster to decelerations than to accelerations (Michon, 1967). Our results are the first neurophysiological evidence for previous hypotheses that behavioral preference for longer step adaptation responses in stroke patients (Roerdink, 2009) and dual task paradigms (Li et al., 2012, Lovden et al., 2008, De Sanctis et al., 2014) is associated with the higher demands of cognitive control and inhibition involved in step shortening.

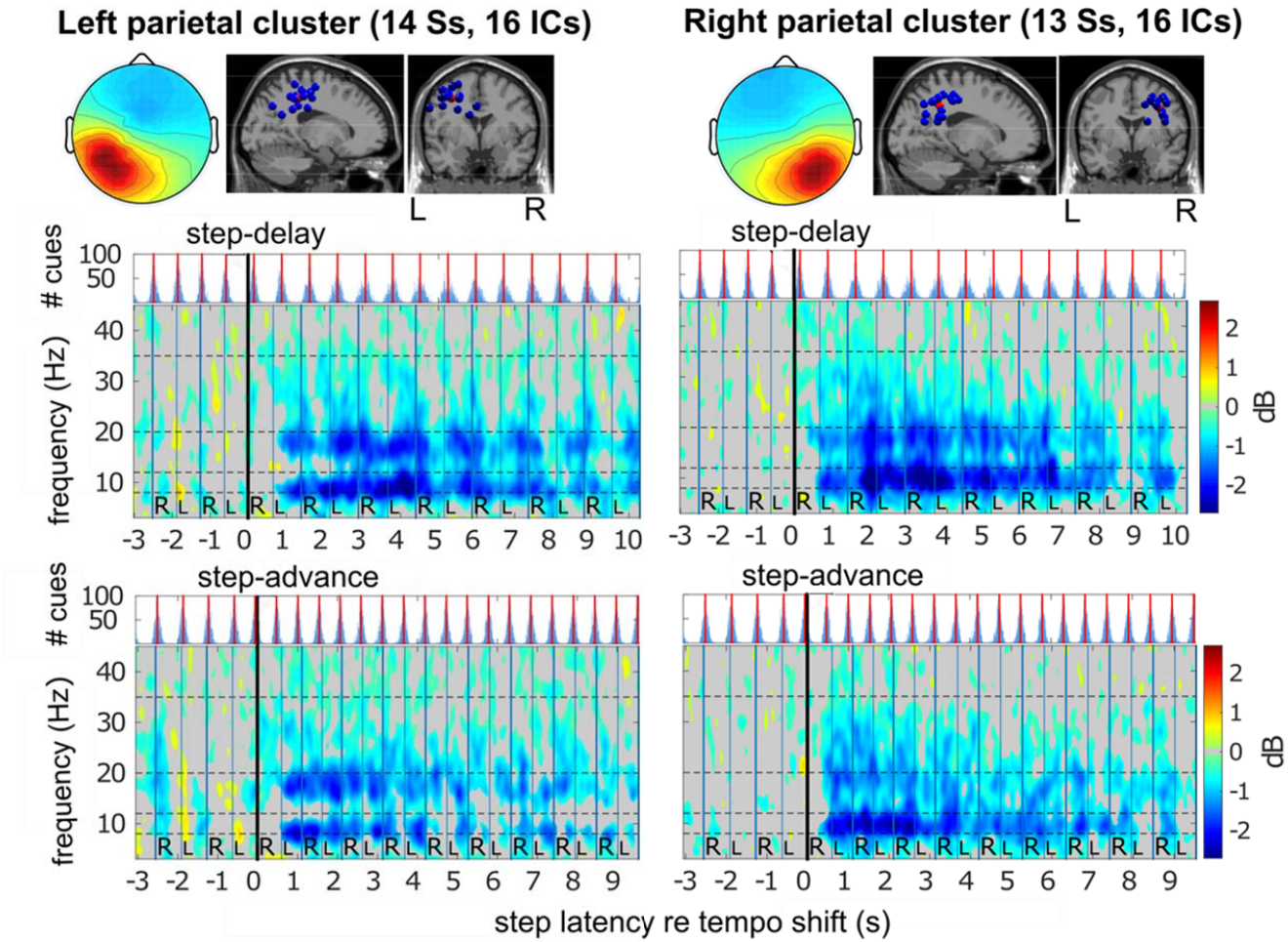

Figure 4.12. Scalp projections, spatial locations, and cluster mean ERSP images for IC source clusters in left and right parietal cortex. *Cluster mean ERSP images for step lengthening and step shortening trials were computed and visualized as in Figure 4. Single-trial spectrograms were time warped to median step latencies for heel strikes -7 to 15 around tempo shift onsets. ERSP images show long lasting, shift-induced decreases in alpha and beta band power that were maximal before heel strikes of the foot* ***contralateral*** *to the cortical location.*

Studies have shown that while right dlPFC is associated with response inhibition (Swann et al, 2009, Aron, 2014) medial and left PFC may relate to error detection (Rubia et al 2003, Ridderinkhof et al., 2004) and motor adjustment (Miller & Cohen, 2000, Wittfoth et al., 2009, Cavanagh et al., 2009, 2010, Kübler et al, 2006) respectively. This lateral dissociation is in line with our results as only the right dlPFC showed a difference between step-advance and step-delay trials, while medial and left PFC showed beta band power increased during both gait accelerations and decelerations.

It has been proposed that frontal cortex interacts with basal ganglia structures during motor suppression, and that this interaction occurs via beta band oscillations (Kühn et al., 2004, Lalo et al., 2008). Beta band synchrony within the basal-ganglia-cortical loop promotes tonic activity that is detrimental to voluntary movement, thus providing further evidence for the role of beta band oscillations in motor inhibition (Jenkinson & Brown, 2011).

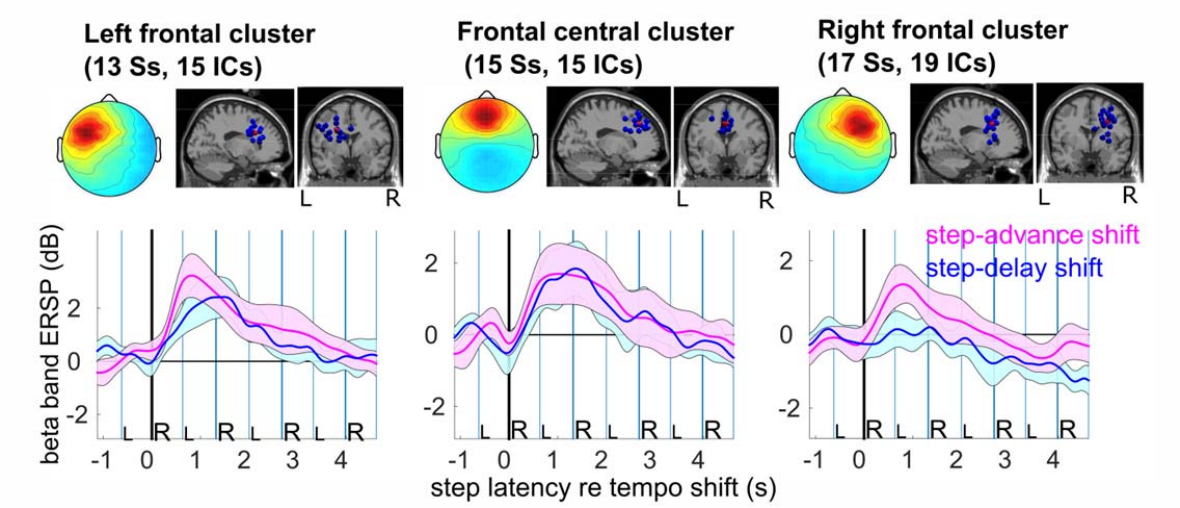

Figure 4.13. Beta band spectral perturbations in frontal clusters. *Individual beta frequency bands were selected for each individual subject as the frequency within the range 14 to 20 Hz having maximal ERSP power variance. For statistical analysis, ERSPs relative to step-advance and step-delay tempo shifts were computed. Heel strike events were time warped to the same (median) latencies in step-delay and step-advance shift trials. Blue and pink lines and areas depict mean beta band power as a function of trial latency and its 95% confidence interval. Only the right frontal cluster shows a significant difference between step advances and step delays as evidenced by the non- overlapping confidence intervals.*

Feedback motor control in parietal and central-midline cortices. Parietal clusters show a prominent and long-lasting decrease in two frequency bands – mu (7 to 12 Hz) and beta (18 to 30 Hz) in (Figure 4.12) while beta band power decrease in medial central regions is short lasting and recruits higher frequencies (up to 35 Hz) (Figure 4.11). This may suggest that both clusters reflect different processes or different stages of gait adaptation. Mu and beta band power desynchronization in left and right PPC was strongest near contralateral heel strikes for up to 17 steps after the shift and may reflect the matching of steps and auditory cues. Since auditory, visual and tactile information converge in parietal regions, PPC has been proposed as sensorimotor interface responsible for multisensory integration with ongoing movements (Buneo et al., 2002, Buneo & Andersen, 2006). Thus PPC may play a key role for

anticipatory motor control by sensorimotor feedback matching (Krause et al., 2012; 2014, Thaut, 2008).

Krause et al. (2014) have shown that inhibition of the PPC interrupts a matching process of anticipated and real sensorimotor feedback during synchronization but not during continuation tapping. In a previous study we showed a decrease in mu and beta band power in PPC during visually guided gait adaptation in a virtual environment suggesting that the PPC is involved in matching steps with visual input (Wagner et al., 2014). Taking into account our current results the role of the PPC in mapping visual representations with motor output in space (Buneo & Andersen, 2006) may possibly be transferable to the matching of a distance in time between auditory and motor events.

Participants made most of their adaptation effort within the first three steps after the cue tempo shifts, with a rapid adaptation of the step period and a gradual reduction in the phase difference between steps and cues. These results are in line with finger tapping studies showing that a small sudden tempo change in the pacing sequence tends to be followed by rapid adaptation of the tapping period accompanied by slow adaptation of tapping phase (Thaut et al., 1998a). Considering the temporal dynamics of beta band changes the temporary frontal beta band power increase we observe may correspond to period adaptation, while long lasting parietal mu and beta band decrease may be related to phase correction. According to Vorberg and Wing (1996), phase correction is a peripheral motor process while period correction involves changing the period of a mental timekeeper that drives the motor response.

Beta band oscillations in temporal prediction. Interestingly, beta band activity in sensory and motor systems seems to reflect anticipatory processes. In the motor system an upcoming action is reflected in decreased motor cortical beta band activity several seconds before execution (Donner et al., 2009), and beta band cortico-spinal coherence increases with decreasing likelihood of an upcoming action (Schoffelen et al., 2005). In the auditory cortex the violation of top-down predictions (the omission of a sound in a regular beat sequence) evokes an increase of beta band power (Fujioka *et al.,* 2009) and may represent an error-related response. Similar to these findings our results also show an alpha and lower beta band power (7 to 20 Hz) increase in a temporal cortex source cluster following tempo shifts (Figure 4.9). Synchronization-continuation tapping studies indicate that beta band power is linked to the development of subjective time or to the guidance of internally driven motor sequences (Bartolo et al., 2014, Bartolo & Merchant, 2015). Precise sensorimotor timing and anticipation of subsequent events is essential in quick adjustment of movements with respect to external changes. Thus the beta band activity we observed could point to a wider function of beta band oscillations in the updating of internal representations for upcoming actions and events (Arnal & Giraud, 2012, Engel & Fries, 2010), to perform corrective motor adjustments.

Summary and future directions. Our results show two distinct beta band oscillatory networks subserving motor and cognitive control. According to our knowledge this is the first study showing neural correlates of these two distinct mechanisms interplaying in the service of gait adaptation. Beta band power increase within the r-dlPFC was modulated by adaptation difficulty. This effect may reflect an involvement of additional control resources for movement-control, and provides the first direct evidence that gait adaptation strategies involving step shortening require more cortical

inhibition/control compared to lengthening. Taking into account our results, deficits in gait adaptation are most probably due to an impairment of prefrontal control guiding motor inhibition. This idea has been previously tested in two TMS studies (del Olmo et al., 2007, Lee et al., 2014). Authors were stimulating right dlPFC with repetitive TMS at 10 Hz (no other frequencies were tested). Both studies have shown temporal improvement of gait and tapping but not Parkinson symptoms. Our results (along with Swann et al., 2009) suggest that stimulation at a higher frequency (16 to 17 Hz) might prove more effective. Such interventions could be used for voluntary motor suppression training with real-time feedback of motor cortical beta oscillations and motor evoked potentials (as proposed in Majid et al., 2015).

5. Discussion and conclusion

5.1. Summary

In order to develop BCIs for gait rehabilitation and to advance lower limb motor rehabilitation therapies, it is fundamental to understand the role of cortical processes involved in human locomotion. The aim of the thesis was therefore to investigate the electrocortical dynamics that accompany functional gait movements and consequently advance the development of BCI technology for post-stroke locomotor rehabilitation therapies.
Furthermore this thesis aimed at uncovering cortical activation patterns related to different rehabilitation approaches to evaluate their efficacy in promoting lower limb recovery. These problems were tackled using high-density electroencephalographic (EEG) recordings and ICA during walking.

The studies in this thesis explored and identified the role of mu, beta and gamma rhythms in steady state gait movements as well as in gait adaptation. Finally, this thesis shows cortical activation relative to different training approaches in gait rehabilitation. These results may be used to provide feedback on optimal activation of motor-cortical networks during the therapy and may also be exploited as a measure to determine the efficacy of certain therapy approaches.

The following paragraphs summarize the main contributions of this thesis.

1. Functional gait movements were shown to be represented in oscillatory neuroelectrical activity. We observed a modulation of low gamma band power (25 to 40Hz) over the premotor cortex relative to the gait cycle. In the same brain area walking induces a mu and beta band suppression during walking compared to standing (Wagner et al., 2012). This study has led to two further publications exploring the role of low (Seeber et al., 2014a) and high (Seeber et al., 2015) gamma rhythms in gait movements, and the reconstruction of gait cycle patterns based on low gamma amplitudes (Seeber et al., 2014b).
2. Active participation is represented by a desynchronization in the mu and beta band over the sensory foot area during robot assisted gait training (Wagner et al., 2012). The results of this study have been exploited in several BCI studies for single trial detection of active participation in gait movements (Solis-Escalante et al., 2012, Wagner et al., 2014b).
3. Interactive movement related feedback in a Virtual Environment (VE) task increases voluntary motor drive and agency during robot assisted gait (Wagner et al., 2014a). This is reflected in a decrease of mu and beta rhythms in premotor and parietal areas during movement related feedback compared to mirror feedback and movement unrelated feedback. Furthermore, low gamma (25 to 40 Hz) gait cycle related modulations in the premotor cortex were shown to be dependent on the VE task.
4. By employing a novel sensorimotor gait synchronization task I show that two distinct beta band oscillatory networks subserving motor and cognitive control interplay in the service of gait adaptation. The results showed mu and beta ERD over premotor and parietal areas relative to

adaptive walking while beta power was transiently increased over frontal areas possibly related to cognitive control (Wagner et al., 2015).

5. Beta band power increase within the right dorsolateral prefrontal cortex was modulated by adaptation difficulty. This effect is the first direct evidence that gait adaptation strategies involving step shortening may require additional cortical control resources compared to lengthening (Wagner et al., 2015).

5.2. Relationship to the state of the art

Advances in signal processing methods (Makeig et al., 2009, Gwin et al., 2020; 2011, Presacco et al., 2011) have led to an increasing number of EEG studies exploring cortical motor control during natural behavior and gait. While some studies have explored the cognitive load of walking by employing dual task paradigms and examining ERPs relative to secondary tasks (Gramann, et al., 2010, de Sanctis et al., 2014, Malcolm et al., 2015), other studies have tried to assess neural correlates related to the actual cortical control of walking (Gwin et al., 2010; 2011, Presacco et al., 2011, Haefeli et al., 2011, Sipp et al., 2013, Peterson et al., 2012, Wagner et al., 2012; 2013; 2014a; 2014b, Seeber et al., 2013; 2014a; 2015).

5.2.1. Gait movements are represented in electrocortical rhythms

Mu and beta desynchronization during gait related to motor readiness*:* Suppression of mu and beta rhythms during the preparation and execution of voluntary movements is a well-established phenomenon and has been shown previously in numerous studies on single limb movements (Jasper and Penfield, 1949, Pfurtscheller and Berghold, 1989, Pfurtscheller and Lopes da Silva, 1999). The studies that were conducted as part of this thesis (Wagner et al., 2012; 2014a; 2015) provide evidence that this principle also holds for whole body movements such as walking.

In Wagner et al. (2012), I show that the active contribution to gait movements is related to the reduction of mu and beta power in sensorimotor areas. Furthermore active walking significantly suppressed mu and beta rhythms (Wagner et al., 2012) in the premotor cortex relative to standing. Further analysis of the same data revealed that mu and beta band synchrony between sensorimotor areas is reduced during active walking compared to standing (Wagner et al., 2013). Single trial connectivity analysis also revealed that information flow between sensorimotor sources is decreased in mu and beta rhythms during active compared to passive walking (Wagner et al., 2014b). Seeber et al. (2013; 2014a) used inverse modeling and individual MRI images to reanalyze the data collected in Wagner et al. (2012) and confirmed that active walking compared to standing enhances mu and beta ERD over sensorimotor areas. Thus, our results provide evidence that mu and beta suppression indeed represent an active state during walking as has been shown for restricted lower limb movements (Crone et al., 1998, Pfurtscheller and Lopes da Silva, 1999, Neuper and Pfurtscheller, 2001, Pfurtscheller et al., 2003, Miller et al., 2007), and suggests that active walking increases the activation of sensorimotor regions and reduces information flow between these areas.

Recent results from other studies further support these findings. Severens et al. (2012), observed a suppression of β oscillations in central sensorimotor areas during walking relative to a non-movement baseline. Furthermore in line with our results another study showed that walking reduces connectivity between sensorimotor areas relative to standing (Lau et al., 2014). Interestingly, recently Bulea et al. (2015) observed mu and beta decrease over sensorimotor and parietal areas relative to active walking on a user-driven treadmill simulating overground locomotion compared to normal treadmill walking.

Low gamma modulations relative to gait cycle phases: Wagner et al. (2012) is the first study that provides evidence of low gamma (25 to 40 Hz) power modulations locked to the gait cycle. Wagner et al. (2014a) demonstrated that these power fluctuations are task dependent and are modified by motor planning during gait adaptation. Seeber et al. (2014a), (using the data from Wagner et al., 2012) identified the same lower gamma band modulations (25 to 40Hz) over central sensorimotor areas. Interestingly a recent study observed significant coherence in the same frequency range (25 to 40Hz) between EEG recordings over foot motor areas at electrode Cz and the anterior tibialis muscle during treadmill walking (Petersen et al., 2012). The time lag between the EEG and the EMG signal suggests that rhythmic cortical activity in this particular frequency band is driving lower limb muscles during walking. The results of Wagner et al. (2012) and Seeber et al. (2014a) show that beta band suppression during active walking relative to standing and low gamma modulation are simultaneously present during walking. In Wagner et al. (2012) these two phenomena appear to be located in the same independent source in the premotor cortex.

Seeber et al., 2015 recently employed a novel frequency clustering method to analyze high gamma activity during walking using the data collected in Wagner et al. (2012). The method employs principal component analysis (PCA) to separate broadband from narrowband frequency activity. He was able to identify high gamma power modulations (70 to 90Hz) located focally in central sensorimotor areas modulating conversely to the low gamma amplitude changes (25 to 40Hz). Interestingly, the authors also uncovered a general sustained increase in high gamma power (60 to 80Hz) in the same areas during walking compared to standing. While beta band synchrony has been shown to be detrimental to voluntary movements gamma band synchrony has been shown to promote motor execution (Jenkinson and Brown, 2011). Thus taking into account the previous findings (Wagner et al., 2012; 2014a, Seeber et al., 2014a), Seeber et al. (2015) proposes that beta suppression and high gamma increase during walking may be related to motor readiness while low and high gamma amplitudes influence the excitability of this state.

Using ICA, Gwin et al. (2011) also reported interstride modulations in the EEG relative to treadmill walking. Our findings however differ from the results by Gwin et al. 2011 in two important points. First, we reported low and high gamma power modulations in restricted frequency bands that modulate conversely relative to the gait cycle. Instead Gwin et al. (2011) report broad band frequency modulations that range from mu to high gamma bands. Second, low and high gamma modulations were observed only over central sensorimotor areas (Seeber et al., 2014a; 2015) and localized to the supplementary motor area (Wagner et al, 2012; 2014a), whereas Gwin et al. (2011) observed broadband intrastride modulations in a wide range of brain areas.

Two distinct beta band oscillatory networks in gait adaptation: Few EEG studies up to now have investigated the neural correlates of gait adaptation strategies. Haefeli et al. (2011) showed an increased event related potential (ERP) in the EEG over prefrontal areas during preparation and performance of steps over obstacles on a treadmill (Haefeli et al., 2011). Recently, Sipp et al. (2013) showed an electroencephalographic theta band increase over cortical areas following loss of balance during walking.

In the second part of this thesis (Wagner et al., 2014a) I show that adaptive walking in an interactive task in a virtual environment decreases mu and beta power in premotor and parietal areas suggesting a higher activation of these areas relative to walking without movement related feedback. The results indicate that visually guided gait adaptation requires increased motor planning and matching of visual and motor information in the parietal cortex. Interestingly a recent study by Lisi & Morimoto, (2015) showed suppression of mu and beta rhythms in parietal areas suggesting a higher activation of these areas during gait speed changes.

In Wagner et al. (2015), perturbations in a regular auditory sequence of cues induced gait adaptations (longer or shorter steps) during treadmill walking. A recent study revealed that stroke patients preferentially use gait adaptation strategies involving longer steps (Roerdink et al., 2009). Walking with a secondary task (Li et al., 2012, Lovden et al., 2008, De Sanctis et al., 2014) also induced participants to take longer strides. These findings have led to the hypothesis that step shortening requires higher cognitive control. The results of our study revealed two distinct beta band oscillatory networks interacting in the adjustment of motor responses during gait adaptation and suggest two different functions of beta band oscillations in gait control. We observed mu and beta band power desynchronization in premotor and parietal cortex expressing a prokinetic state related to motor readiness (as in Pfurtscheller & Da Silva, 1999, Neuper et al., 2006, Wagner et al., 2012; 2014a, Seeber et al., 2014a) and synchronization of beta band oscillations in the frontal cortex related to cognitive top-down control (as in Bushman et al., 2012, Swann et al., 2009). Furthermore beta band power increase within the right dorsolateral prefrontal cortex was modulated by the difficulty of the employed gait adaptation strategy (step lengthening - easier, step shortening - more difficult). This effect may reflect higher demand of cognitive control and inhibition related to movement-control during step shortening.

5.3. Towards Brain-Computer Interface technology for gait rehabilitation

Several single trial analysis based on the results of Wagner et al. (2012) have been carried out aiming at the automatic detection of active participation during gait training. Solis Escalante et al. (2012), attempted single trial classification of active and passive walking from the EEG recorded during robotic assisted gait training. Using common spatial patterns (CSP) (Ramoser et al., 2000, Blankertz et al., 2000) and Laplacian filters, accuracies reached levels better than chance in all participants. Differences between active and passive walking emerged mostly in mu (6 to 14 Hz) and low gamma (34 to 42 Hz) frequency bands over the somatosensory cortex in foot and hand areas. The study showed also that Laplacian filters may be a better choice in artifact prone environments as they are less sensitive to noise than CSP.

Based on measures that quantify interactions between brain areas in Wagner et al. (2014b) we aimed at differentiating active and passive gait movements in single trial EEG. The data was pruned using ICA to account for muscle and movement artefacts. Single trial connectivity between brain sources was estimated in three frequency bands: mu (7 to 12Hz), beta (15 to 21Hz), and a subject specific frequency band ranging from 24 to 40 Hz selected according to previous findings in Wagner et al. (2012). Using connectivity features, classification accuracies were above chance in all subjects, and outperformed previous results employing band power features (Solis-Escalante et al., 2012) by 10%. Interestingly, using an adaptive treadmill a recent study by Lisi & Morimoto (2015) distinguished volitional gait speed changes and steady state walking based on mu and beta suppression in the EEG over parietal areas.

In Seeber et al. (2014b) we concentrated on the decoding of gait cycle phases from EEG signals using a Laplacian Cz derivation and low gamma amplitude modulations (based on the results in Wagner et al., 2012; 2014a, Seeber et al., 2014a). The method succeeded in reconstructing gait cycle patterns in all of ten participants during passive walking and 8/10 participants during active walking. This difference is possibly due to the higher artefact contamination during active walking.

Other studies that aimed at implementing BCI technology for gait rehabilitation, have mainly exploited low frequency signals recorded from the EEG such as movement related cortical potentials (MRCPs) that have been shown to be associated with the preparation and execution of movement (Toro et al., 1994, Birbaumer et al., 1999, Waldert et al., 2008). Presacco et al. (2011) employed EEG signals between 0.1 to 2 Hz and linear autoregressive models to decode kinematics of the ankle, knee and hip joints during human treadmill walking. Bulea et al. (2014) differentiated between the motor preparation of standing-up, sitting-down and standing quietly using delta-band (0.1-4Hz) EEG features. Another recent study attempted single trial classification of walking and pointing direction (Velu et al., 2013) using a feature space from 0.5 to 50 Hz in the EEG. Their analysis showed that frequencies between 0.5 and 2Hz were most critical for discriminating the classes. Based on the combination of MRCPs and ERD single trial EEG features, Sburlea et al. (2015) were able to detect motor preparation related to self-paced gait initiation. Using an online approach with automatic artefact rejection based on ICA, Jiang et al, 2014 were able to detect step initiation from single trial MRCPs in the EEG over electrode Cz.

All of the studies summarized above however have been carried out offline except for Jiang et al. (2014), due to the lack of efficient automatic artefact rejection methods operating in real time. Recently, several online artefact rejection methods to recover electrocortical dynamics during movement have been proposed. Lau et al. (2012) implemented the Weighted Phase Lag Index, that quantifies the phase lag between EEG signals to recover ERPs during walking. Mullen et al. (2013) proposed an 'artifact subspace reconstruction method' that uses templates of clean EEG recordings and PCA to identify and remove high amplitude artefacts in the EEG. Recently Daly et al. (2014) implemented a method based on wavelet decomposition and SOBI ICA to remove artefactual frequency components. A method that has been shown to effectively remove broadband frequency noise during walking has recently been introduced by Seeber et al. (2015). The method allows for the separation of broad band and narrow band frequency activity by frequency clustering and PCA.

A limitation of the above listed studies is the lack of EEG recordings from individuals with stroke as all of the studies have been carried out in able bodied participants. Thus there is a clear need to translate results to real rehabilitation applications in clinical settings. Recently, two studies have implemented a BCI translating motor imagery based EEG features in mu (13 to 16Hz) and beta bands (23 to 28Hz) to actual gait movements in one paraplegic patient with spinal cord injury (Do et al., 2013, King et al., 2014, 2015). The patient was able to walk via BCI induced gait movements in a robot assisted gait orthosis (Do et al., 2013) and over ground using functional electric stimulation (FES) of the leg muscles (King et al., 2014, 2015).

5.4. Limitations

Recently, two studies (Castermans et al., 2014, Kline et al., 2015) showed that movement artefacts in the EEG during walking can involve frequencies from 1 up to 150 Hz. Castermans et al. (2014) compared EEG and accelerometer signals recorded from the head during walking and found similar time-frequency properties between the two signals in bands extending up to 150 Hz. Furthermore in line with previous results from Gwin et al. (2010), the analysis of Castermans et al. (2014) showed that up to 15 harmonics of the step frequency can contaminate the EEG signal. Kline et al. (2015) blocked electrophysiological signals by using a silicone swim cap as a nonconductive layer to record pure movement artefact with EEG electrodes. In line with Castermans et al. (2014), they found that movement artefacts recorded at scalp electrodes contain frequencies from 1 up to 150 Hz and depend on speed and electrode locations.

It has been shown that EMG appears in frequencies above 20Hz (Muthukumaraswamy et al., 2013, Castermans et al., 2013) and spreads from marginal to central EEG channels during walking (Gramann et al., 2010, Gwin et al., 2010, 2011, Seeber et al., 2014a). Instead, electrocortical oscillations relative to motor processing synchronize or decrease in narrow frequency bands such as mu (7 to12Hz) and beta (15 to 30Hz) as has been shown by many EEG and electrocorticography (ECoG) studies during restricted lower limb movements (Pfurtscheller et al., 1997, Crone et al., 1998, Miller et al., 2007, Müller-Putz et al., 2007) and walking (Wagner et al., 2012; 2014a, Severens et al., 2012, Seeber et al., 2014a). Due to these distinct properties in frequency range and spatial distribution of cortical signals, biological noise and mechanical artefacts, proper application of signal processing methods allows to separate these sources (Gwin et al., 2010, Wagner et al., 2012, Seeber et al., 2014a; 2015).

The low and high gamma gait related power modulations we observed (Wagner et al, 2012, 2014a, Seeber et al, 2014a; 2015) can be considered biologically plausible as they are restricted to a narrow frequency band. They are also localized to a confined cortical area. Furthermore, Petersen et al, 2012 demonstrated that motor cortical rhythmic activity in the 25 to 40Hz range drives leg muscles during walking. Our results are consistent with the observation by Petersen et al., (2012), both in cortical location as in frequency range. Furthermore our results on beta band suppression and high gamma increase related to movement execution are in line with previous findings in literature on the functional role of these rhythms in motor execution. Additionally, participants in our studies walked at relatively slow walking speeds that have been previously shown to not be heavily affected by artefacts (Gwin et

al., 2010). This accumulated evidence indicates that the observed frequency specific power modulations in the EEG are of cortical origin.

Gwin et al. (2010) also demonstrated that during steady state walking the EEG signal is affected most considerably in the frequencies below 4 Hz. Wagner et al. (2012) showed that power in frequencies from 1 to 2Hz was significantly increased in the raw EEG, compared to ICA pruned EEG, during walking. This power increase is probably related to movement artifacts as the frequency range 1 to 2 Hz contains the step frequency of participants. However BCI studies using low frequency modulations from 1 to 4Hz as in Presacco et al. (2011), do not report on the use of particular artefact rejection methods to remove artifactual components in the EEG. This may suggest that decoding of gait kinematics using low frequency modulations (1 to 2Hz) and linear autoregressive models as shown by Presacco et al. (2011) is based on periodic movement artefacts in the EEG. Furthermore recently Antelis et al. (2013) showed significant correlations between randomly shuffled low frequency EEG signals and upper limb kinematics. The authors suggest that prior reports of reconstructing limb kinematics based on low frequency EEG signals are simply due to the mathematical properties of the linear regression model.

5.5. Conclusion and outlook

In the area of movement dysfunctions, gait has clearly emerged as a major field of investigation. This rising interest is partly due to the awareness that autonomy in daily living is highly dependent on the recovery and conservation of mobility and the avoidance of falls. On the other hand advances in neuroimaging methods and signal processing tools have opened a new avenue to examine the neural correlates of gait.

In this respect the studies, that were conducted as part of this thesis demonstrate that EEG based neuroimaging provides an excellent methodology by which the underlying cortical dynamics of motor and cognitive control processes involved in full body movements such as upright gait can be studied. This allows to overcome the traditional, rather artificial paradigms in neuroimaging studies that generally examine only a very restricted sample of the behavior controlled by the brain, such as a finger button press. This is crucial in the case of neurorehabilitation for gait disorders to discover the relation between anomalies in neural dynamics and associated impairments in gait parameters.
Importantly, the results of this thesis make a fundamental contribution to the understanding of the cortical mechanisms and the role of neuronal rhythms in gait control. This knowledge can be used to develop a model of the cortical control of gait in health and disease and may also contribute to a better understanding of cortical reorganization related to lower limb movements.

This thesis also provides directions for the use of non-invasive electrical neuroimaging in the clinical neurorehabilitation of gait and shows that the extent of cortical activation patterns during gait training can be assessed through neuronal oscillations. This measurement may be used as a tool to assess motor cortical excitability throughout the therapy in clinical settings and identify cortical correlates of plasticity. This thesis provides an exemplary framework for future electrophysiological para-

digms to investigate neuronal dynamics linked to movement disorders and their recovery. This may open new prospects in the development of neuroscientifically informed motor therapies.

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Seeber, M., Wagner, J., Scherer, R., Solis Escalante, T., Müller-Putz, G. (2014b) Reconstructing gait cycle patterns from non-invasive recorded low gamma modulations. In: *Proceedings of the 6th International Brain-Computer Interface Conference, Graz, Austria.*

Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., & Müller-Putz, G. R. (2015). High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle. *NeuroImage, 112*, 318-326.

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Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R. & Müller-Putz, G.R. (2013). Robot assisted walking affects the synchrony between premotor and somatosensory areas. In: *Proceedings of the BMT 2013, Graz, Austria*.

Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C. & Müller-Putz, G.R. (2014a). It's how you get there: Walking down a virtual alley activates premotor and parietal areas. *Frontiers in Human Neuroscience, 8, 93*

Wagner, J., Billinger, M., Solis Escalante, T., Brunner, C., Neuper, C., Scherer, R., & Müller-Putz, G.R. (2014b). Active participation during walking reduces single trial connectivity in sensorimotor areas. *Proceedings of the 6th International Brain-Computer Interface Conference, Graz, Austria.*

Wagner, J., Makeig, S., Gola, M., Neuper, C. & Müller-Putz, G.R. (2015) Distinct beta band oscillatory networks subserving motor and cognitive control during gait adaptation. *Submitted*

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Appendix

A. List of Publications

Journal articles

Wagner, J., Makeig, S., Gola, M., Neuper, C. & Müller-Putz, G.R. (2015) **Distinct beta band oscillatory networks subserving motor and cognitive control during gait adaptation.** *Submitted*

Seeber, M., Scherer, R., **Wagner, J**., Solis-Escalante, T., & Müller-Putz, G. R. (2015). **High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle.** *NeuroImage, 112, 318-326*.

Scherer, R., Billinger, M., **Wagner, J.,** Schwarz, A., Hettich, T., Bolinger. E., Lloria Garcia, M. & Müller-Putz, G. (2015). **Thought-based row-column scanning comunication board for individuals with cerebral palsy.** *Annals of Physical and Rehabilitation Medicine*

Seeber, M., Scherer, R., **Wagner, J**., Solis Escalante, T. & Mueller-Putz, G. (2014). **EEG beta suppression and low gamma modulation are different elements of human upright walking.** *Frontiers in Human Neuroscience*, *8*, *485.*

Wagner, J, Solis-Escalante, T, Scherer, R, Neuper, C & Müller-Putz, GR (2014) **It's how you get there: Walking down a virtual alley activates premotor and parietal areas.** *Frontiers in Human Neuroscience, 8, 93*

Wagner, J, Solis-Escalante, T, Grieshofer, P, Neuper, C, Müller-Putz, GR & Scherer, R (2012) **Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects.** *NeuroImage, 63, 3, 1203–1211*

Conference proceedings

2014

Wagner, J., Billinger, M., Solis Escalante, T., Brunner, C. Neuper, C., Scherer, R., Müller-Putz, G. (2014) **Active participation during walking reduces single trial connectivity in sensorimotor areas.** *Proc. of the 6th International Brain-Computer Interface Conference, Graz, Austria*.

Seeber, M., **Wagner, J.**, Scherer, R., Solis Escalante, T., Müller-Putz, G. (2014) **Reconstructing gait cycle patterns from non-invasive recorded low gamma modulations.** *Proc. of the 6th International Brain-Computer Interface Conference, Graz, Austria*.

Scherer, R., **Wagner, J**., Billinger, M., Müller-Putz, G. (2014). **Online artifact reduction and sequential evidence accumulation enhances robustness of thought-based interaction.** *Proc. of the 6th International Brain-Computer Interface Conference, Graz, Austria*.

Scherer, R., **Wagner, J.**, Billinger, M., Müller-Putz, G., Raya, R., Rocon de Lima, E., Mohamad, Y., Hettich, T., Bolinger. E., Iosa, M., Cincotti, F., Londrai, A., Mesquita, J., Lloria Garcia, M., Belda, J. (2014). **Augmenting communication, emotion expression and interaction capabilities of individuals with cerebral palsy.** *Proc. of the 6th International Brain-Computer Interface Conference, Graz, Austria*.

2013

Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2013) **Robot assisted walking affects the synchrony between premotor and somatosensory areas.** *in: Proceedings of the BMT 2013, Graz, Austria.*

Seeber, M., Scherer, R., **Wagner, J.**, Solis Escalante, T., Müller-Putz, G. (2013) **Spatial-spectral identification of μ and β EEG rhythm sources during robot-assisted walking.** *in: Proceedings of the BMT 2013, Graz, Austria.*

2012

Scherer, R, **Wagner, J.**, Moitzi, G, & Müller-Putz, GR (2012) **Kinect-based detection of self-paced hand movements: Enhancing Functional Brain Mapping paradigms.**, *IEEE Engineering in Medicine and Biology Annual Conference 2012*.

Solis Escalante, T, **Wagner, J**., Scherer, R, Grieshofer, P, & Müller-Putz, G (2012). **Assessing participation during robotic assisted gait training based on EEG: feasibility study.** *Proceedings of the 3rd TOBI Workshop Bringing BCIs to End-Users: Facing the Challenge - Evaluation, User Perspective, User Needs, and Ethical Questions*, *61-62.*

Holzinger, A, Scherer, R, Seeber, M, **Wagner, J**, & Müller-Putz, G (2012). **Computational Sensemaking on Examples of Knowledge Discovery from Neuroscience Data: Towards Enhancing Stroke Rehabilitation.** *International Conference on Information Technology in Bio- and Medical Informatics - ITBAM 2012*, *166-168.*

Conference abstracts

2015

Wagner, J., Makeig, S., Neuper, C. & Müller-Putz, G.R. (2015). **Keeping in step: Entrainment of theta and low-gamma activity in the brain with gait rhythm.** *Society for Neuroscience annual meeting, Chicago, USA*

2014

Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2014) **Acoustically induced gait perturbations reveal neural correlates of step adaptation strategies.** *OHBM Annual Meeting. Hamburg, Germany*

Seeber, M., Scherer, R., **Wagner, J.**, Solis Escalante, T., Müller-Putz, G. (2014) **High and low γ oscillations in the sensorimotor feet area are conversely modulated by the gait cycle.** *OHBM Annual Meeting. Hamburg, Germany*

Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2014) **Neural correlates of motor planning during robot assisted walking in able bodied subjects.** *Cutting EEG (Symposium on cutting-edge methods for EEG research), Berlin, Germany*

Seeber, M., **Wagner, J.**, Scherer, R., Solis Escalante, T., Müller-Putz, G. (2014) **Spectral component analysis reveals high-γ sources during gait.** *Cutting EEG (Symposium on cutting-edge methods for EEG research), Berlin, Germany*

2013

Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2013) **Neural correlates of auditory-motor synchronization during walking to the beat.** *1st international Mobile Brain/Body Imaging (MoBI) conference*, *Delmenhorst, Germany*

Wagner, J., Solis Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2013) **Interaction between parietal and premotor areas is disrupted during visually guided gait adaptation.** *OHBM Annual Meeting. Seattle, WA, USA*

Seeber, M., Scherer, R., **Wagner, J.**, Solis Escalante, T., Müller-Putz, G. (2013) **EEG beta band sources modulated by gait cycle during robot-assisted walking.** *OHBM Annual Meeting. Seattle, WA, USA*

2012

Wagner, J., Solis-Escalante, T., Neuper, C., Müller-Putz, G., Scherer, R. (2012) **Suppression of the central Mu and Beta Rhythms during Robot assisted Walking in Humans.** *8th FENS Forum of Neuroscience, Barcelona, Spain*

Scherer, R, Grieshofer, P, Enzinger, C, Seeber, M., **Wagner, J.**, Solis-Escalante, T & Müller-Putz, GR (2012) **Predicting Functional Stroke-Rehabilitation Outcome by means of Brain-Computer Interface Technology: The BCI4REHAB Project.** *World Congress for NeuroRehabilitation.*

Solis Escalante, T., Faller, J.; Kaiser, V., **Wagner, J**., Scherer, R., Müller-Putz, G. (2012) **BCI research toward stroke rehabilitation at TU Graz.** *World congress on medical physics and biomedical engineering. Peking*

2010

Wagner, J., Ihme, K., Gaertner, G., Kothe, C., Zander, T.O. (2010). **Benchmarking common BCI algorithms for fast-paced HMS applications.** *Fourth International BCI Meeting, Carmel, CA, June 2010*

Invited talks

2015

Wagner, J. (2015) **Keeping in step: Entrainment of low-gamma activity in the brain with gait rhythm.** *The Max Planck Institute for Cognitive Neuroscience, Leipzig, Germany*

Wagner, J. (2015) **Keeping in step: Entrainment of low-gamma activity in the brain with gait rhythm.** *The Albert Einstein College of Medicine, New York, USA*

2013

Wagner, J., Solis-Escalante, T., Neuper, C., Scherer, R., Müller-Putz, G. (2013) **Hirnaktivität während roboterunterstütztem Gehen** *16th annual meeting of the ÖGSF (Österreichische Schlag-anfall Gesellschaft - Austrian society for stroke)*

B. Core publications

B.1. Author contributions

This section lists the approximate amount of work each author has contributed to each of the three main publications.

1. Wagner, J., Solis-Escalante, T., Grieshofer, P., Neuper, C., Müller-Putz, G., & Scherer, R. (2012**). Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects.** *Neuroimage*, *63*(3), 1203-1211.

   Wagner J, (70%), Solis-Escalante,T. (12%), Grieshofer, P. (1%), Neuper, C. (5%), Müller-Putz, G.R. (5%), Scherer, R. (7%)
   Conceived and designed the experiment: JW, TSE, CN, RS; Performed research: JW, TSE; Contributed materials: PG; Analyzed the data: JW; Wrote the paper: JW, TSE, GMP, RS

2. Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C., & Müller-Putz, G. (2014). **It's how you get there: walking down a virtual alley activates premotor and parietal areas.** *Frontiers in Human Neuroscience*, *8*.

   Wagner J, (70%), Solis-Escalante,T. (13%), Neuper, C. (5%), Scherer, R. (7%), Müller-Putz, G.R. (5%)
   Conceived and designed the experiment: JW, TSE, CN, RS; Performed research: JW, TSE; Analyzed the data: JW; Wrote the paper: JW, TSE, GMP, RS

3. Wagner, J., Makeig, S., Gola, M., Neuper, C., & Müller-Putz, G. (2015). **Distinct beta band oscillatory networks subserving motor and cognitive control during gait adaptation**. *Submitted*

   Wagner J, (70%), Makeig, S. (15%), Gola, M. (5%), Neuper, C. (5%), Müller-Putz, G.R. (5%)
   Conceived and designed the experiment: JW, GMP; Performed research: JW; Analyzed the data: JW, SM; Wrote the paper: JW, SM, MG, CN, GMP

B.2. Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able bodied subjects

Wagner, J., Solis-Escalante, T., Grieshofer, P., Neuper, C., Müller-Putz, G., & Scherer, R. (2012). *Neuroimage*, *63*(3), 1203-1211. *doi:10.1016/j.neuroimage.2012.08.019*

NeuroImage 63 (2012) 1203–1211

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects

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ARTICLE INFO

Article history:
Accepted 5 August 2012
Available online 14 August 2012

Keywords:
Neurorehabilitation
Robotic gait training
Locomotion
Brain monitoring
Electroencephalography

ABSTRACT

In robot assisted gait training, a pattern of human locomotion is executed repetitively with the intention to restore the motor programs associated with walking. Several studies showed that active contribution to the movement is critical for the encoding of motor memory. We propose to use brain monitoring techniques during gait training to encourage active participation in the movement.

We investigated the spectral patterns in the electroencephalogram (EEG) that are related to active and passive robot assisted gait. Fourteen healthy participants were considered. Infomax independent component analysis separated the EEG into independent components representing brain, muscle, and eye movement activity, as well as other artifacts. An equivalent current dipole was calculated for each independent component. Independent components were clustered across participants based on their anatomical position and frequency spectra. Four clusters were identified in the sensorimotor cortices that accounted for differences between active and passive walking or showed activity related to the gait cycle. We show that in central midline areas the mu (8–12 Hz) and beta (18–21 Hz) rhythms are suppressed during active compared to passive walking. These changes are statistically significant: mu ($F(1, 13) = 11.2$ $p \leq 0.01$) and beta ($F(1, 13) = 7.7$, $p \leq 0.05$). We also show that these differences depend on the gait cycle phases. We provide first evidence of modulations of the gamma rhythm in the band 25 to 40 Hz, localized in central midline areas related to the phases of the gait cycle. We observed a trend ($F(1, 8) = 11.03$, $p \leq 0.06$) for suppressed low gamma rhythm when comparing active and passive walking. Additionally we found significant suppressions of the mu ($F(1, 11) = 20.1$ $p \leq 0.01$), beta ($F(1, 11) = 11.3$ $p \leq 0.05$) and gamma ($F(1, 11) = 4.9$ $p \leq 0.05$) rhythms near C3 (in the right hand area of the primary motor cortex) during phases of active vs. passive robot assisted walking.

To our knowledge this is the first study showing EEG analysis during robot assisted walking. We provide evidence for significant differences in cortical activation between active and passive robot assisted gait. Our findings may help to define appropriate features for single trial detection of active participation in gait training. This work is a further step toward the evaluation of brain monitoring techniques and brain–computer interface technologies for improving gait rehabilitation therapies in a top–down approach.

Introduction

Locomotor disorders represent a major burden after stroke. The ability to walk safely and independently at an acceptable speed and therefore regaining a level of functional gait (Perry, 1992), is an important factor in allowing patients to lead an autonomous and self-determined life. However the underlying mechanisms of motor recovery of gait in stroke survivors are still not well understood (see Calautti and Baron, 2003; Forrester et al., 2008 for a review). In the last years, rehabilitation therapy with robotic gait trainers has been often presented as an addition to therapist assisted gait training. In robot assisted gait training, a pattern of human locomotion is executed repetitively. This is assumed to restore motor functions of gait by restoring the motor programs associated with walking (Galen et al., 2011; Wirz et al., 2001). An advantage over traditional gait training where therapists manually facilitate stepping in patients is the increased number of movement repetitions that are possible (Hornby et al., 2008). Manual assisted therapy is limited due to the physical demand placed on therapist. Hence the efficacy of the locomotor therapy may be adversely affected (Hornby et al., 2008). One advantage of manual assisted over automated therapy is however that patients are only assisted-as-needed. Robot assisted gait training can lead patients to

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http://dx.doi.org/10.1016/j.neuroimage.2012.08.019

move passively, as the robot executes enough force to impose movements of their legs and is not sensitive to the effort exerted by the patients (Hidler and Wall, 2005; Israel et al., 2006). Several studies showed that active contribution to a movement is critical for the encoding of motor memory (Kaelin-Lang et al., 2005; Lotze et al., 2003). For example, Lotze et al. (2003) found that active training improved motor performance and increased corticomotor excitability in comparison with passive training. Training effectiveness and motor recovery could therefore be improved by monitoring patients' performance and encouraging them to participate actively in the movement.

Different methods have been proposed to measure active participation of patients in robot assisted gait training. These methods use physiological and mechanical variables like force executed by the patient (Lünenburger et al., 2007), heart rate (Koenig et al., 2011) and oxygen uptake (Pennycott et al., 2010) to assess patient participation. Oxygen uptake and heart rate variability are rather unspecific indicators of cooperation to the training as they will reflect any increase in physical activity. Force sensors provide more information about the kinematics of the movement, however, up to now output from force sensors has not been shown to be related to the benefit of a movement for locomotor recovery (Lünenburger et al., 2007).

We propose to assess active participation in the gait training based on brain monitoring techniques. In this way, cooperation to the movement and the amount of cortical activation can be verified directly from the patient's electroencephalogram. In the future this measurement may also help to examine the therapeutic benefits of the movement and determine neurophysiological correlates of improvements in motor performance (Boyd et al., 2007). In gait rehabilitation therapy up to now there are few objective criteria for measuring functional improvements. Brain monitoring techniques that surveille the patients' cortical pattern during therapy could be therefore useful to relate changes of cortical activation in certain brain areas to clinical scales coding functional improvements. This could also help to evaluate the efficiency of therapeutic interventions.

Up to now, few studies have investigated direct neural correlates during actual gait in humans, mainly due to the restrictions that movement artifacts pose for neuroimaging techniques, i.e. EEG, functional magnetic resonance imaging (fMRI), and near infrared spectroscopy (NIRS). The cerebral correlates of gait have been partly studied using isolated movements, e.g., leg or foot movements that represent a part of human locomotion (Dobkin et al., 2004; Luft et al., 2005; Metha et al., 2009; Müller-Putz et al., 2007; Neuper and Pfurtscheller, 2001; Pfurtscheller et al., 1997; Raethjen et al., 2008; Sahyoun et al., 2004; Wieser et al., 2010). Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have tried to measure brain activity before and after walking (Fukuyama et al., 1997; Hanakawa et al., 1999; la Fougere et al., 2010), and have revealed that besides medial primary sensorimotor areas, also the premotor cortex, parietal cortex, basal ganglia and cerebellum seem to be contributing to gait.

Direct evidence comes from several NIRS studies that have measured cerebral activity during actual gait (Miyai et al., 2001; Suzuki et al., 2004, 2008). These studies showed that walking increases cerebral activity bilaterally in the medial primary sensorimotor cortices, the supplementary motor area (SMA), and the prefrontal cortex. Several studies have shown the feasibility of recording EEG during treadmill walking. A low resolution EEG study (Haefeli et al., 2011) found that during the preparation and the performance of obstacle stepping on a treadmill the EEG signal was enhanced in the prefrontal cortex compared to normal walking. Presacco et al. (2011) showed that frequencies below 2 Hz in the human EEG contain information about angular and linear kinematics of the hip, knee, and ankle joints during treadmill walking. Previously Fitzsimmons et al. (2009) had shown that it is possible to decode 3D coordinates of leg joints during treadmill walking from neurons in monkey motor cortex. Recently Gwin et al. (2010) published the first study showing intrastride activity in the human EEG related to treadmill walking. The authors used independent component analysis (ICA) to separate artifacts, muscle, and brain sources, and demonstrated that the method allows for a high spatial resolution analysis of EEG recorded during whole body movements.

The purpose of this work was to explore cortical patterns related to robot assisted walking and establish the feasibility of recording EEG during automated gait training. A second goal was to examine the neurophysiological correlates of active participation during robot assisted gait training. To these ends we investigated spectral patterns in the EEG related to active and passive walking in a gait robot.

Materials and methods

Participants

Fifteen healthy volunteers with no neurological or locomotor deficits participated in this study. One subject's data was excluded because of heavy muscle artifact contamination of the EEG recordings. The remaining data of fourteen subjects (eight males and six females, age 22 to 28 years avg: 24.3, SD: 2.7, right handed) was analyzed. The experimental procedures were approved by the ethical committee of the Medical University Graz. Each subject gave informed consent before the experiment.

Experimental design and procedure

Participants completed eight runs of robot assisted walking (four in each of two walking conditions) and three runs of upright standing. Experiments were carried out in the Rehabilitation Clinic Judendorf-Strassengel (Austria), using the robotic gait orthosis Lokomat (Hocoma, Switzerland). Fig. 2 illustrates the experimental setup. The Lokomat is a robotic driven gait orthosis that includes electrical drives in knee and hip joints and incorporates a motorized treadmill and body weight support system. Parameters of the Lokomat were adjusted according to the common practice in clinical therapy with the help of physical therapists having experience with the Lokomat for several years. Walking speed was kept low and adjusted to the participants leg length according to the formula: $speed = 0.54(leg)/27.8$ where *leg* is the participant's leg length in cm and the *speed* is computed in km per hour. Walking speed ranged from 1.8 to 2.2 km per hour between participants lying below the comfortable overground walking speed at around 5 km/h (Bohannon, 1997). This walking speed is slightly below the walking speeds used in other studies that measured EEG during treadmill walking (Gwin et al., 2010: 2.4 km/h; Presacco et al., 2011: 2.9 km/h and 4.5 km/h). Body weight support (BWS) was adjusted to a participant specific minimum with the help of experienced physical therapists. This adjustment was necessary to ensure a correct activation of foot switches (left/right heel) used to track the gait cycle and at the same time allow passive walking that requests a certain level of BWS. This adjustment resulted in a body weight support that was in all participants below 30%. The Lokomat was run in a control mode with 100% guidance force. The movement tasks consisted of active and passive walking. In the active walking condition, the participants were instructed to walk independently in the gait robot on the treadmill supporting their own weight during the stance phase as far as the body weight support allowed it. Participants were asked to walk at the speed of the treadmill and to avoid pushing against the knee and hip orthosis. Passive walking demanded participants to let their legs be moved by the robot, and not to oppose the movement. In a control condition, subjects were instructed to stand in the Lokomat and support their own weight. Body weight support was kept constant between conditions. In all conditions participants were asked to relax their arms and rest them on the sidebars of the Lokomat. Each walking session lasted 6 min, each rest session lasted 3 min. Six minutes of robot assisted walking consisted in 150 to 225 gait cycles (one gait cycle lasting from 1.6 to 2.4 s depending on the participant's leg length). We defined one gait cycle as the interval between two right leg heel contacts. Before starting the experimental

sessions subjects were asked to train active and passive walking in the gait robot for some minutes to get used to the orthosis and the movements. After a short acclimation period (about 2 min for each walking task), all subjects reported that walking in the device felt sufficiently comfortable and the kinematic trajectory of the movement tasks was easy to follow. Conditions were randomized. In all conditions, participants were asked to look straight ahead, not to close their eyes for prolonged periods of time, and to blink normally.

Data acquisition

We combined four 32-channel amplifiers (two BrainAmp DC and two BrainAmp MR plus amplifiers, Brainproducts, Munich, Germany) to record the EEG from 120 electrode sites. The montage was in accordance with the 5% 10/20 system (EasyCap, Germany) (Oostenveld and Praamstra, 2001). Electrode locations that extended below the conventional 10–20 spherical layout included PO9, POO9, OI1, OI2, POO10, PO10, I1, Iz, and I2. Reference and ground electrodes were placed on the left and right mastoids respectively. Electrode impedance was less than 10 kΩ. Three-dimensional electrode coordinates were measured with the Zebris Elpos system (Noraxon, USA) on a screening day prior to the actual measurement. We took precautions to correctly position the electrode cap over the participants' head, to ensure that the electrode coordinates did not change.

Electromyogram (EMG) was recorded from biceps femoris and tibialis anterior muscles of both legs using standard adhesive disposable Ag/AgCl electrodes. EMG was recorded monopolarly, using left and right mastoids as reference and ground. EMG bipolar derivations were calculated offline. EEG and EMG were sampled to 2.5 kHz, high pass filtered at 0.1 Hz, and low pass filtered at 1 kHz. Foot contact was measured by mechanical foot switches placed over the calcaneus bone at the heel of both feet. These switches produced the markers for the gait cycle: heel on, heel off (relative to each leg).

EEG analysis

EEG data analysis was performed in Matlab using EEGLAB 8.0.3.5b (Delorme and Makeig, 2004) (available online http://www.sccn.ucsd.edu/eeglab), based on Gwin et al. (2010). Considering the noise present in robotic gait training, Infomax independent component analysis was used to account for possible contamination of the EEG. Before submitting the EEG data to an ICA decomposition the data had to be preprocessed accordingly and was subjected to a rigorous artifact rejection following the methods of Gwin et al. (2010) and Onton et al. (2006).

The data was high pass filtered at 1 Hz [zerophase FIR filter order 7500] to minimize slow drifts, and low pass filtered at 200 Hz [zerophase FIR filter order 36]. After removing channels with prominent artifacts identified by visual inspection, channels with probability more than five times the standard deviation from the mean across all channels were rejected. On average 112 EEG channels were kept for further analysis for each subject (range: 94–118, SD: 6). Then, a common average reference was computed from the remaining channels. The continuous EEG data was visually inspected for non-stereotyped artifacts (e.g. swallowing, electrode cable movements, etc.). Affected segments were rejected from further analysis. Typical artifacts caused by eye movements, eye blinks and muscle tension were kept in the analysis. These artifacts produce a stereotyped pattern in the EEG data, and can be separated by ICA into only a few independent components.

The data was segmented into epochs of 0.5 s. Outliers were removed by determining the probability distribution of values across the data epochs (avg. ±5 SD). On average, 76% of the gait cycles of each participant's EEG data remained in the analysis (range: 64–91%, SD: 9).

After these preprocessing steps, an adaptive independent component analysis mixture model algorithm (AMICA) (Palmer et al., 2006, 2008) was run on the data. AMICA is a generalization of the Infomax algorithm (Bell and Sejnowski, 1995; Makeig et al., 1996) and multiple mixture (Lee et al., 1999; Lewicki and Sejnowski, 2000) ICA approaches. It separates EEG signals into independent components (ICs) assumed to be spatially static and maximally temporally independent (Makeig et al., 1996). One ICA decomposition was computed for each subject over all conditions (active walking, passive walking and rest).

A best-fitting single equivalent current dipole, was calculated for the scalp projection for each independent source using a standardized three-shell boundary element head model (BEM) implemented in the DIPFIT toolbox of EEGLAB (Delorme et al., 2012; Oostenveld and Oostendorp, 2002). Electrode positions measured from the participants' head were co-registered and aligned with a standard brain model (Montreal Neurological Institute, MNI, Quebec, Canada). Further analysis considered only ICs if the associated dipoles were located within the head and explained more than 90% of variance of their scalp projection.

The remaining independent components (ICs) were visually inspected considering power spectrum and event-locked time course to identify ICs which isolate activations related to brain activity. This procedure led to an average of 14 brain related ICs per participant (ranging between 6 and 18 ICs) used in further analyses.

ICs across subjects were clustered using EEGLAB routines (Delorme and Makeig, 2004). Feature vectors were created coding differences in dipole location, power spectral density (1–45 Hz), and scalp projection of each IC. The dimensionality of the resulting joint vector was reduced to ten principal components, using the principal component analysis (PCA). Vectors were clustered with k-means (with $k = 19$). 'Outlier' components further than three standard deviations from any of the resulting cluster centers were relegated to a separate cluster.

Analysis of artifact contamination to the surface signal

We computed the power spectral density (PSD) using Welch's method for different stages of artifact removal for the representative channels F10, Cz, C3, C4, and P10 (see Fig. 1). 1) Channel based artifact removal, 2) after rejecting ICs representing non physiological artifacts such as line noise and movement artifacts, and 3) after rejection of all ICs that were classified as non cortical activity. Stage 1) corresponds to the preprocessed EEG data before it is submitted to ICA. For stage 2), clusters related to muscle and eye activity were selected according to their dipole locations, time course and frequency spectra and then together with brain related components backprojected to the EEG. For stage 3) the brain related ICs were backprojected to the EEG. A 1×3 ANOVA was computed with factor artifact rejection stage (levels 1–3), for frequency ranges of 1–2 Hz and 30–40 Hz. The low frequency band (1–2 Hz) was selected as it encompassed the step frequency for all subjects, and the high frequency range (30–40 Hz) was chosen as frequencies at 30 Hz or higher are likely to contain muscle activity. Additionally event related spectral perturbations (ERSP) (Makeig, 1993) were computed for each subject and channels Cz and Pz and then averaged for artifact rejection stage 1). ERSPs are generally calculated, computing the power spectra over a sliding latency window and normalizing these spectograms dividing by their respective mean baseline spectra. These normalized transforms are then averaged over trials. To generate gait cycle ERSPs, for each subject and channel single trial spectograms were computed and timewarped using a linear interpolation function, to align the timepoints for the right and left heel strikes over epochs following the methods by Gwin et al. (2010). Visualization of relative changes in spectral power was obtained by subtracting the average log spectrum for all gait cycles within a channel from each single-trial log spectogram according to Gwin et al. (2010). These normalized spectograms were averaged obtaining grand average ERSPs for each condition and each channel over subjects. Significant deviations from the average gait cycle log spectrum were computed with a bootstrapping method (Delorme and Makeig, 2004).

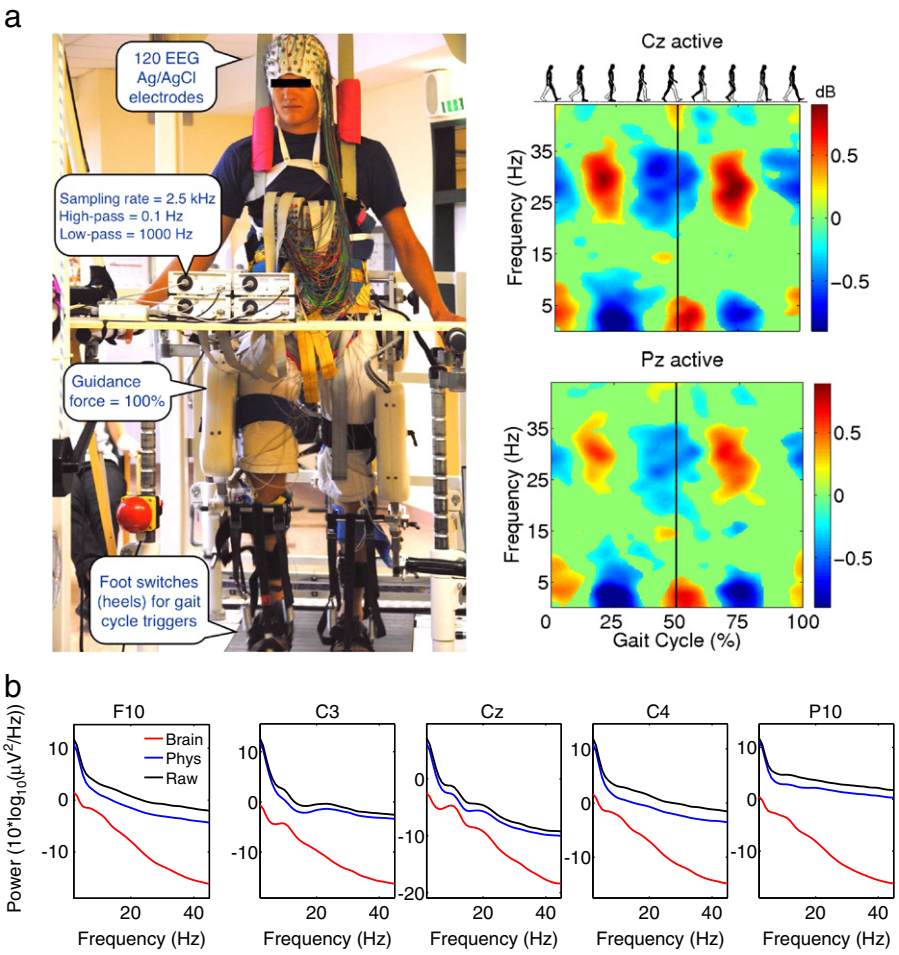

Fig. 1. Experimental setup; average EEG channel PSD at F10, C3, Cz, C4 and P10 and average ERSP plots for Cz and Pz. (a) (From left to right) Experimental setup: subject walking in the Lokomat gait orthosis with body weight support. The amplifiers for EEG recordings are fixed on a board in front of the participant. The orthosis is adapted and fixed to the participant's legs with the help of an experienced physical therapist; average ERSP plots over all subjects for channels Cz and Pz showing significant changes in spectral power during the gait cycle for active walking. Non-significant differences relative to the full gait cycle baseline ($p \leq 0.05$) are masked in green (0 dB). The right leg heel contact marks the beginning and end of the gait cycle, the vertical line signs the temporally aligned event of left heel-strike (50%). (b) For three artifact rejection stages: 1. Channel based artifact removal (black line), 2. After removing non physiological artifacts (blue line) 3. Retaining only activity classified as cortical (red line), for channels F10, C3, Cz, C4 and P10. Panel a: (Part of this image was modified from http://atec.utdallas.edu/midori/Handouts/walkingGraphs.htm).

Clusters of cortical ICs

For clusters of brain related sources the PSD was computed for each source and condition using Welch's method and a one way ANOVA was computed to compare the types of movement (active walking, passive walking and rest) for each cluster. ERSPs were computed for each independent source using the same procedure described previously for channels. Here for each source, single trial spectograms were computed and timewarped and then the average log spectrum for all gait cycles within a source from each single-trial log spectogram was subtracted. Then these spectograms were averaged for each condition and each cluster (Delorme and Makeig, 2004). To assess differences between active and passive walking independent component ERSPs were calculated in three frequency bands: mu (8–12 Hz), beta (15–21 Hz) and gamma (25–40 Hz); using a common baseline (the average over all gait cycles) for active and passive walking trials. The frequency bands were selected by visual inspection of the clusters' mean power spectra. A 2×7 ANOVA with factors "Movement Type" (active vs. passive walking) and "Gait cycle phase" (seven gait cycle phases according to Perry (1992)) was computed. Following the definition by Perry (1992) the gait cycle can be divided into: stance phase (0–60%) and swing phase (60–100%). These phases are subdivided into: Loading response (0–10%), mid stance (10–30%), terminal stance (30–50%) and preswing (50–60%) for the stance phase; and initial swing (60–73%), midswing (73–87%) and terminal swing (87–100%) for the swing phase. The gait cycle phases were always calculated relative to the right leg, providing the framework for a whole cycle. All significance values were Greenhouse–Geisser corrected in cases where the assumption of sphericity was violated. Post-hoc tests were computed using simple paired t-tests, controlling for false discovery rate (Benjamini and Yekutieli, 2001) with a significance level set a priori at 0.05.

Results

Analysis of artifact contamination to the surface signal

Sensor based analysis revealed significant differences between artifact removal stages in frequency ranges of 1–2 Hz and 30–40 Hz computed with PSD for all electrodes tested (F10, C3, Cz, C4, P10) (see Fig. 1, for significance values see Table 1). Post hoc tests revealed that in these frequency ranges all artifact removal stages are significantly different from each other at the 0.05 level, except for Cz at 1–2 Hz. Fig. 1 shows average ERSP maps for electrodes Cz and Pz computed for artifact removal stage 1. Both channels show significant changes

($p \leq 0.05$) from baseline relative to the phases of the gait cycle in the lower gamma band (25–40 Hz) during active walking visible in the channel average ERSPs.

Clusters of cortical ICs

Four clusters revealing differences between active and passive walking were identified and accounted for activity in the sensorimotor areas. The number of subjects and sources contained in each cluster and Talairach coordinates of cluster centroids is displayed in Table 2.

Cluster A, located in the premotor cortex, showed significant changes ($p \leq 0.05$) from baseline relative to the phases of the gait cycle in the lower gamma band (25–40 Hz) during active and passive walking visible in the cluster average ERSPs (see Fig. 2). This cluster presented a significant difference in the PSD between active walking, passive walking and rest in all three frequency bands mu: ($F(2, 16) = 11.03$, $p \leq 0.01$), beta: ($F(2, 16) = 9.03$, $p \leq 0.01$) and gamma ($F(2, 16) = 10.5$, $p \leq 0.01$). Post hoc tests revealed significant differences between active walking vs. rest ($p \leq 0.05$) and passive walking vs. rest ($p \leq 0.05$) in the mu and in the gamma band. Differences in single gait cycle phases between active and passive walking did not reach significance however a trend ($F(1, 8) = 11.03$, $p \leq 0.06$) was evident for the gamma band.

Cluster B, located in the foot area of the sensory cortex, showed significant differences in power spectral density between conditions in the mu band ($F(2, 26) = 22.28$, $p \leq 0.01$), in the beta band ($F(2, 26) = 25.7$, $p \leq 0.01$), and in the gamma band ($F(2, 26) = 18.61$, $p \leq 0.01$) (see Fig. 3). Post hoc tests revealed a significant difference ($p \leq 0.05$) between active and passive walking in the beta band. Additionally significant differences were present between active walking vs. rest ($p \leq 0.05$) and passive walking vs. rest ($p \leq 0.05$) in the mu, in the beta and in the gamma band. We found a significant difference in gait cycle phases between active and passive walking in the mu ($F(1, 13) = 11.2$, $p \leq 0.01$) and in the beta band ($F(1, 13) = 7.7$, $p \leq 0.05$). Post hoc tests revealed significant differences ($p \leq 0.05$) from 0 to 73% and from 87 to 100% of the gait cycle in the mu band and from 10 to 50% of the gait cycle in the beta band (see Fig. 4).

For cluster C a significant difference between conditions in the PSD was observed only in the beta band ($F(2, 22) = 7.16$ $p \leq 0.05$). Post hoc tests revealed a significant difference ($p \leq 0.05$) between active walking and standing. For cluster D located in the right hand area of the primary motor cortex there is a significant difference in PSD in the mu ($F(2, 18) = 8.15$, $p \leq 0.05$), beta ($F(2, 18) = 13.7$, $p \leq 0.01$), and gamma band ($F(2, 18) = 4.8$, $p \leq 0.05$) between the three conditions (see Fig. 3). Post hoc tests revealed significant differences ($p \leq 0.05$) between passive walking and standing for the mu, beta and gamma bands and between active walking and standing ($p \leq 0.05$) for the beta band. In single gait phases a significant difference between active and passive walking was observed for this cluster in the mu ($F(1, 11) = 20.1$, $p \leq 0.01$), the beta ($F(1, 11) = 11.3$, $p \leq 0.05$) and the gamma band ($F(1, 11) = 4.9$, $p \leq 0.05$). Post hoc tests revealed that this difference in the mu band was present and significant ($p \leq 0.05$) during the whole gait cycle. In the beta band comparison of single gait phases revealed significant differences ($p \leq 0.05$) from 0 to 73% of the gait cycle. In the gamma band the preswing phase (50–60%) was found to be significantly different (see Fig. 4).

Table 1
Significant differences between artifact rejection stages.

Channel	1–2 Hz	30–40 Hz
F10	$F(2, 26) = 30.75$, $p \leq 0.01$	$F(2, 26) = 24.27$, $p \leq 0.01$
C3	$F(2, 26) = 7.1$, $p \leq 0.05$	$F(2, 26) = 13.04$, $p \leq 0.01$
Cz		$F(2, 26) = 7.0$, $p \leq 0.05$
C4	$F(2, 26) = 26.15$, $p \leq 0.01$	$F(2, 26) = 6.67$, $p \leq 0.05$
P10	$F(2, 26) = 8.27$, $p \leq 0.05$	$F(2, 26) = 13.39$, $p \leq 0.01$

Table 2
Clusters of independent sources obtained with ICA.

Cluster	Location of cluster centroid	Talairach coordinates (x, y, z)	Number of subjects (S) and ICs
A	Premotor cortex	−1, −4, 63	9 S, 9 ICs
B	Somatosensory cortex foot area	6, −36, 56	12 S, 14 ICs
C	Left primary motor cortex hand area	−35, −17, 47	10 S, 10 ICs
D	Right primary motor cortex hand area	36, −14, 48	10 S, 12 ICs

Discussion

Analysis of artifact contamination to the surface signal

Comparison of different artifact rejection stages shows for the PSD of channels F10, C3, Cz, C4, P10 that after IC based artifact rejection power is significantly reduced at 1–2 Hz and 30–40 Hz. Average channel PSD plots also show that only with artifact rejection stage three we are able to reveal a peak in the mu band (8–12 Hz) at channels C3 and Cz. These results show that sensor-level analysis can only partly, deal with such complex, artifact-laden signals. ERSP plots at Cz and Pz show a similar activation pattern in the gamma band as cluster A. Obviously, artifact contamination at electrodes Cz and Pz is moderate and can be controlled by normalizing the spectograms when computing ERSPs. However, spatial resolution is poor as the pattern spreads from Cz to Pz. The good quality of the data can be explained by the slow walking speed and the fact that the upper body of participants in the Lokomat is partly immobilized by the body weight support. Gwin et al. (2010) showed that at slow walking speeds (2.9 km/h) artifact contamination is moderate and average channel PSD computed before and after IC based artifact removal gives similar results.

Clusters of cortical ICs

Four clusters were identified in the sensorimotor cortices that are related to robot assisted walking. We demonstrate that significant differences between active and passive walking are evident in the foot area of the sensory cortex and in the right primary motor cortex hand/arm area. Additionally we show that lower gamma band activity in the premotor cortex is related to the gait cycle during robot assisted walking.

The PSD for cluster A located in the premotor cortex shows a peak in the mu (8–12 Hz) and in the beta (18–21 Hz) band for the rest condition. The activity in these bands is suppressed during active and passive walking. This suggests that during the movement conditions this brain area is more active than during standing. Lower gamma band frequency modulations in the premotor cortex show an event related desynchronization (ERD) (Pfurtscheller and Lopes da Silva, 1999) during initial contact (0–10%) terminal stance and preswing (40–60%) and terminal swing (90–100%) and an event related synchronization (ERS) during midstance (20–30%) and during midswing (70–80%) in the average cluster gait cycle ERSPs during active and passive walking. Thus the ERD occurs before, during and after left and right heel strikes, which correspond to the period when the opposite leg is prepared for leaving the ground. The ERD could therefore represent a preparation for the transition between stance and swing phase. On the contrary, ERS occurs inside these phases when one of the feet is flat on the ground. The activation pattern during active walking seems to be more consistent and stronger than during passive walking, however differences between the conditions do not reach significance. There is a trend in the gamma band suggesting that these changes are more pronounced during active walking. The similar activation pattern in the gamma band related to the active

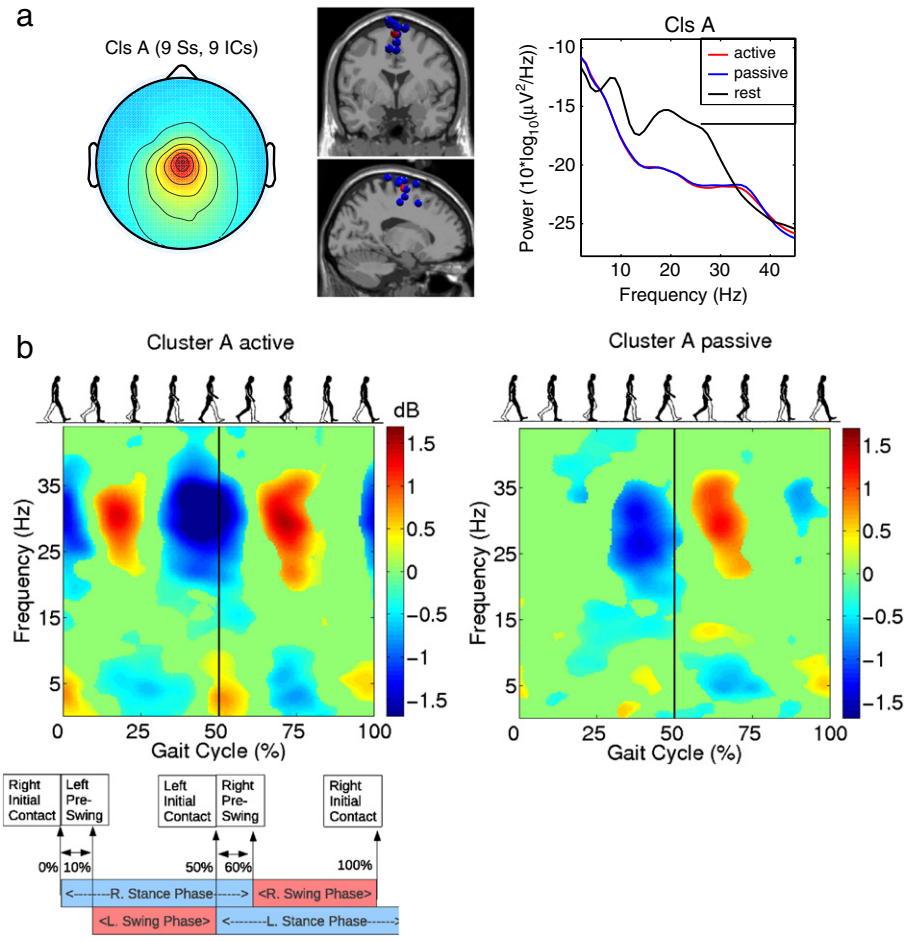

Fig. 2. Scalp projection, dipole locations, PSD and ERSPs for cluster A, located in the premotor cortex. (a) (From left to right) Cluster average scalp projection; dipole locations of cluster ICs (blue spheres) and cluster centroids (red spheres)visualized in the MNI brain volume in coronal and sagittal views; gait cycle PSD for active and passive walking and standing; (b) average cluster ERSP plots showing significant changes (relative to the full gait cycle baseline ($p \leq 0.05$)) in spectral power during the gait cycle for active walking (bottom left), and passive walking (bottom right). Non-significant differences are masked in green (0 dB). The right leg heel contact marks the beginning and end of the gait cycle, the vertical line signs the temporally aligned event of left heel-strike (50%).
Part of this image was modified from http://atec.utdallas.edu/midori/Handouts/walkingGraphs.htm.

and passive gait cycle could be explained by a similar activation pattern of leg muscles in both types of movements. Wieser et al. (2010) showed that leg muscle activation during assisted lower limb movement occurs with a similar time course but with smaller amplitude compared to active movement. Several studies show that patients with complete para-/tetraplegia and infants afferent input from load receptors and from hip joints lead to a locomotor-like leg muscle activation pattern (Dietz, 2002; Dietz et al., 2002; Pang and Yang, 2000). The Lokomat gait orthosis moves hip and knee joints and reduces the load on participants' legs only partly, therefore it is probable that during passive walking lower limb muscles are activated by these afferences.

Central midline activity in the lower gamma band has been previously related to muscle activation during upper and lower limb movements. In line with a study by Raethjen et al. (2008), activation was concentrated on the central midline area. Raethjen et al. (2008) observed that coherence between 15 and 30 Hz related to isometric contraction of the calf muscles during bilateral anti-phase rhythmic foot movements. Other studies have demonstrated that coherence between cortex and muscle in the gamma band is most evident during maximal voluntary muscular contraction and during movement (Brown, 2000; Mima et al., 2000). Also increases in EEG beta activity (40 Hz) during brisk self paced movements (Pfurtscheller and Neuper, 1992; Pfurtscheller et al., 1993) as well as during sustained movements have been shown. A decrease in gamma (35–45 Hz) has been observed during passive relaxation over the corresponding somatotopic locations of primary sensorimotor areas (Alegre et al., 2003). Considering these findings the observed activation and deactivation in the lower gamma band over central midline areas during walking might be related to sensorimotor processing of the lower limbs in the complex motor pattern of human locomotion. A number of studies on rhythmic movements, such as walking and running in animals have shown that the movements are generated by a spinal network, and merely the initiation and modification of the rhythmic activity are controlled by supraspinal structures (Grillner, 1998; Rossignol et al., 2006). Nevertheless, to what degree human locomotor activity is generated by such a spinal network and which influence the cortex has on such a pattern generator, are unknown. Additionally it is not clear to what degree walking in a robotic gait orthosis differs from natural walking on a surface or on a treadmill.

The walking speed was around 2 km/h lying below the comfortable overground walking speed (5 km/h) (Bohannon, 1997). Other studies show that muscle activation and kinematics during Lokomat walking, differ from common treadmill walking (Hidler and Wall, 2005; Hidler et al., 2008). Therefore it is possible that the gamma band activity is related to sensorimotor processing required by the specific walking task in the orthosis.

This would also explain the differences to the results of Gwin et al. (2010) who already showed intrastride changes in the EEG during walking on a treadmill. Contrary to our results, the authors found a similar

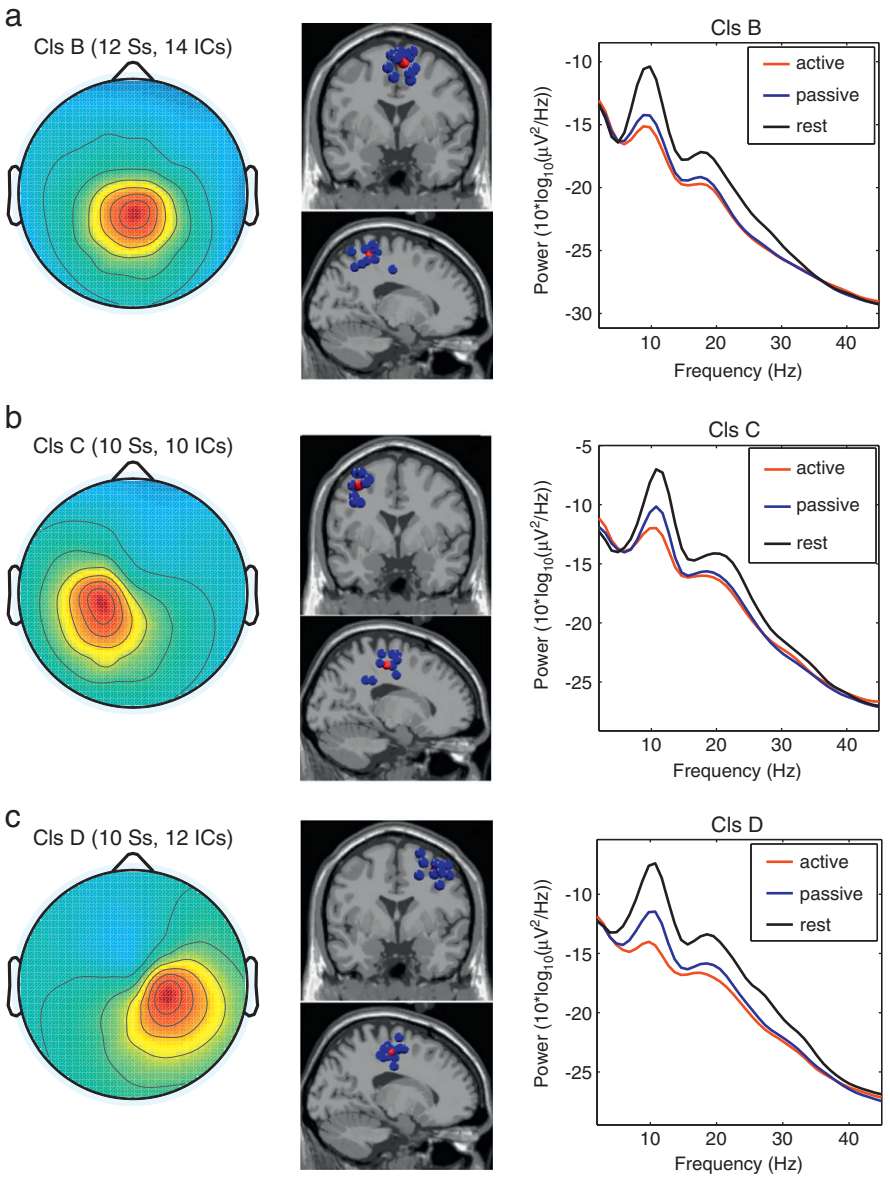

Fig. 3. Scalp projection, spatial location and power spectra of independent component clusters. (a) Cluster B located in the sensorimotor cortex, foot area; (b) Cluster C located in the left primary motor cortex (hand area); (c) Cluster D located in the right primary motor cortex (hand area). From left to right in each row: Cluster average scalp projections; dipole locations of cluster ICs (blue spheres) and cluster centroids (red spheres) visualized in the MNI brain volume in coronal and sagittal views; PSD for active and passive walking and standing. For all clusters a difference in PSD between active and passive walking and standing in the mu and in the beta range can be observed.

pattern related to the gait cycle phases in different regions of the brain that were present over a broad range of frequencies (1–200 Hz). Also the activation and deactivation in Gwin et al. (2010) show a different time course compared to our present results. We observed a decrease in power during the right and left heel strikes in lower gamma band activity, while Gwin et al. (2010) found an increase in power over a broad range of frequency bands during this interval. However compared to our study the walking task differed substantially, as subjects in Gwin et al. (2010) were moving freely without restrictions on the treadmill, supporting their own weight and the walking speed was higher (2.9 km/h and 4.5 km/h). However they report that they did not find significant differences in their results due to these two walking speeds.

Power in the mu and beta bands in the foot/leg area of the sensory cortex (cluster B) was significantly decreased during active compared to passive walking. The cluster is located in the right hemisphere, and the activity therefore relates to the left leg and can be interpreted as an increased activation. This is in line with previous findings. Müller-Putz et al. (2007) observed a greater ERD (Pfurtscheller and Lopes da Silva, 1999) in the mu band during active vs. passive foot movement over central sensorimotor areas most pronounced at electrode position CPz and adjacent electrodes (Cz, C2 and Fcz). Additionally, a PET study (Christensen et al., 2000) and a recent fMRI study (Hollnagel et al., 2011), measuring brain activity during pedaling, showed a higher activation during active compared to passive movements in central primary sensorimotor and premotor areas. fMRI studies on active and passive ankle dorsiflexion (Dobkin et al., 2004; Sahyoun et al., 2004) found similar results. Additionally we found that this increased activation is specific to gait cycle phases (see Fig. 4). For the alpha band this difference is significant between 0 and 73% and from 87 to 100% of the right leg gait cycle. This corresponds to the swing phase and parts of the stance phase of the left leg. The non significant period corresponds to the midstance phase of the left leg when the left foot is flat on the ground.

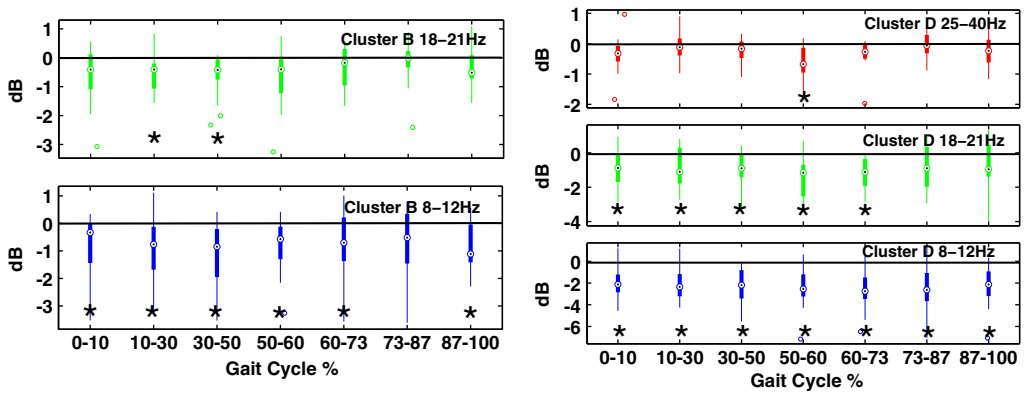

Fig. 4. Boxplots showing differences (active minus passive walking) in normalized average spectral power for the single gait cycle phases. The edges of the box mark the 75th percentiles, black dots the median. Whiskers sign the range of values, outliers are plotted as empty circles. Significant differences are marked with * for $p \leq 0.05$ and ** for $p \leq 0.01$; these difference plots are displayed for Cluster B in the mu and beta bands (left) and Cluster D, in the mu beta and gamma bands (right).

In the beta band a significant difference between 10 and 50% of the right leg gait cycle is evident. This corresponds to the midswing and terminal swing phase of the left leg. Presacco et al. (2011) already showed suppression in PSD in the mu band (8–12 Hz) during precision walking on a treadmill compared to standing. Additionally they showed that low frequencies (0.1–7 Hz) have higher power during walking compared tor rest. However these differences are not significant and not related to a specific brain area (the PSD is averaged over all channels).

Additionally, we found a significant decrease in the mu, beta and gamma bands during active compared to passive walking in the right primary motor cortex hand area. The activity relates to the left arm and can be interpreted as an increased activation. For the mu band this difference is constant across the gait cycle, which suggests dissimilarity in the gait cycle average spectrum during active vs. passive walking. During active walking beta band activity was significantly reduced in the terminal stance, the preswing and the initial swing phases of the right leg gait cycle. Gamma band power was found to be significantly reduced in the preswing phase during active walking (see Fig. 4). During these phases, in overground walking, the left arm moves forward following the movement of the right leg. Studies show that arm swing is an inherent part of human gait (Fernandez Ballesteros et al., 1965). Different beneficial effects of arm swing during locomotion have been presumed, among others its contribution to stability during walking (Ortega et al., 2008), or its role in gait by reducing vertical ground reaction moments and thereby reducing the energetic costs related to walking (Collins et al., 2009; Li et al., 2001; Witte et al., 1991). Although subjects were instructed to relax their arm muscles, they may have involuntarily contracted the muscles that usually make part of arm swing in locomotion. Fernandez Ballesteros et al. (1965) have shown that muscular activity in the upper limbs related to stepping was present even when swinging of the arms was inhibited. Unpublished data recorded in a follow up study where we measured EMG from the arms (posterior deltoid and the flexor carpi radialis) during active robot assisted gait, shows that arm muscle activity is rhythmically related to the gait cycle. In this study subjects were also resting their arms on the siderails of the Lokomat and had the instruction to relax their arms. Miyai et al. (2001) compared cerebral activities evoked during gait, alternating foot movements and arm swing using NIRS. These authors showed that during walking cerebral activity was increased bilaterally in the central primary sensorimotor area and the SMA. This activation was spread over a larger area of the cortex when compared to the simple alternation of foot movements. In addition, they comment on unpublished data according to which the activation patterns of gait with arm swing did not differ from those of gait with subjects holding the siderails by both hands. Taking into account these findings, cortical activity related to arm swing during walking could provide important information about active participation in gait training.

Conclusion

We demonstrate that it is possible to identify cortical activity related to lower limb movements in robot assisted gait that account for differences between active and passive walking. We show that power in the mu and beta bands over central midline areas is significantly reduced during active walking. We also show that this decrease depends on gait cycle phases. This decrease might be related to sensory processing of the lower limbs. We provide first evidence for cortical activity localized in the premotor cortex in the lower gamma band that is related to the gait cycle phases in robot assisted walking. Additionally, there is a trend for decreased gamma power in this brain area during active robot assisted walking probably related to movement planning and/or sensorimotor processing. Additionally, we find significantly decreased alpha, beta and gamma power in the right hand area of the primary motor cortex. Further work has to examine whether these findings can be used to define features for single trial detection of active participation in gait training. This implies in a next phase to investigate our current results in patients.

This work is a further step toward the evaluation of brain monitoring techniques for improving gait rehabilitation therapies in a top–down approach (Belda-Lois et al., 2011). Our results show that EEG recordings may be a powerful tool to monitor cortical activation during automated locomotor rehabilitation. This could help to relate changes in brain activity to functional improvements and determine the effects of therapeutic interventions.

Acknowledgments

This work was partly supported by the European Union research project BETTER (ICT-2009.7.2-247935) and the Land Steiermark project BCI4REHAB. The authors are thankful with Georg Schaffhauser and Pamela Holper for assistance during the experiments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.08.019.

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B.3. STUDY II: It's how you get there: walking down a virtual alley activates premotor and parietal areas

Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C., & Müller-Putz, G. (2014). *Frontiers in human neuroscience, 8*. *doi: 10.3389/fnhum.2014.00093*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 February 2014
doi: 10.3389/fnhum.2014.00093

It's how you get there: walking down a virtual alley activates premotor and parietal areas

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Voluntary drive is crucial for motor learning, therefore we are interested in the role that motor planning plays in gait movements. In this study we examined the impact of an interactive Virtual Environment (VE) feedback task on the EEG patterns during robot assisted walking. We compared walking in the VE modality to two control conditions: walking with a visual attention paradigm, in which visual stimuli were unrelated to the motor task; and walking with mirror feedback, in which participants observed their own movements. Eleven healthy participants were considered. Application of independent component analysis to the EEG revealed three independent component clusters in premotor and parietal areas showing increased activity during walking with the adaptive VE training paradigm compared to the control conditions. During the interactive VE walking task spectral power in frequency ranges 8–12, 15–20, and 23–40 Hz was significantly ($p \leq 0.05$) decreased. This power decrease is interpreted as a correlate of an active cortical area. Furthermore activity in the premotor cortex revealed gait cycle related modulations significantly different ($p \leq 0.05$) from baseline in the frequency range 23–40 Hz during walking. These modulations were significantly ($p \leq 0.05$) reduced depending on gait cycle phases in the interactive VE walking task compared to the control conditions. We demonstrate that premotor and parietal areas show increased activity during walking with the adaptive VE training paradigm, when compared to walking with mirror- and movement unrelated feedback. Previous research has related a premotor-parietal network to motor planning and motor intention. We argue that movement related interactive feedback enhances motor planning and motor intention. We hypothesize that this might improve gait recovery during rehabilitation.

Keywords: neurorehabilitation, robotic gait training, locomotion, motor planning, electroencephalography, interactive feedback, gait adaptation

1. INTRODUCTION

Gait recovery is a major rehabilitation goal in post-stroke therapy. Impairments in normal gait affect balance, stride length, walking speed, obstacle avoidance and endurance. These factors often lead to an increased risk of falls and related injuries (Said et al., 1999). In consequence, affected individuals are not able to react adequately and promptly to demands within their environment, which hinders them in performing activities of daily living autonomously (Duncan et al., 1998).

Much has been discussed about optimal training strategies in rehabilitation and different therapy approaches. Several key features including the form and intensity of motor training are assumed to support neural plasticity in motor learning. In gait rehabilitation extensive training can be provided by using a robotic gait orthosis that allows a high number of movement repetitions (Lum et al., 2002; Mehrholz et al., 2013). However, robotic rehabilitation alone generates a highly repetitive and monotonous practice environment that requires little effort from the individual. Findings on discrete upper limb movements indicate that active performance in the training is more effective for motor learning (Lotze et al., 2003; Kaelin-Lang et al., 2005). Furthermore several studies suggest that the individual's motivation in the training is one of the critical factors in determining the therapy outcome (Maclean and Pound, 2000; Liebermann et al., 2006). It has been argued that a more interactive and demanding learning context, might enhance the individual's motivation and promote active participation in the motor task. Virtual Environments (VEs) provide a convenient solution to these ends as different kinds of motor tasks with various degrees of difficulty can easily be implemented (Holden, 2005; Liebermann et al., 2006). Recent studies suggests that VE can in fact promote active participation during robotic gait training. Brütsch et al. (2010, 2011) and Schuler et al. (2011) showed that training with VE significantly increased active participation during robot assisted gait in children with various neurological gait disorders and healthy controls. Active participation was assessed using biofeedback values from hip and knee torques (Brütsch et al., 2010, 2011) and electromyographic activity of the lower limbs (Schuler et al.,

2011). Other research suggests that VE combined with robot assisted lower limb training has a greater effect on improving gait parameters such as balance, speed, and endurance in individuals after stroke than robot-assisted training alone (Jaffe et al., 2004; You et al., 2005; Mirelman et al., 2009, 2010).

However, so far the underlying neurophysiological processes that are elicited by motor related feedback in a VE during gait training and their relevance to the relearning of motor skills have not been investigated. Active participation and voluntary drive in movements have been shown to be crucial for motor learning (Lotze et al., 2003; Kaelin-Lang et al., 2005). But how does the notion of voluntary drive translate to the movement of gait? In general voluntary movements have been defined as two different kinds of subjective experiences: "intention" which relates to the phase of movement planning and "agency" describing the feeling that one's own movement has caused a specific effect (Tsakiris et al., 2010). These feelings can be promoted by feedback in a VE. Findings also indicate that the experience of agency is related to the presence of perceptual and sensory feedback about the effects of motor actions in the physical world (Blakemore et al., 2002). Thus the feeling of agency can be increased by enhancing feedback to motor actions in a VE. Investigations on upper limb movements reveal a sensorimotor network of premotor-parietal cortices that is related to motor awareness and intention (Sirigu et al., 2003; Berti et al., 2005; Tsakiris et al., 2010), (for a review see Haggard, 2008). However, walking is a rhythmic and highly automated movement and it is not clear which parts of the movement are controlled by the cortex, the brain stem and central pattern generators in the spinal cord (Armstrong, 1988; Grillner et al., 1998). Hence motor awareness and intention most likely differ between walking and discrete upper limb movements. In animals motor areas of the cortex are only activated during gait initiation and gait adaptation, but not during unperturbed gait (Armstrong, 1988; Drew et al., 2008).

Few studies in humans have investigated motor preparation during gait. Recently we compared active to passive walking in a gait robot and found a trend for differences in sensorimotor EEG rhythms over the premotor cortex additionally to differences over sensory areas (Wagner et al., 2012). Wieser et al. (2010) studied evoked potentials related to gait like movements during an upright position. They found that the cortical activity over sensorimotor areas was highest shortly before a change of direction between the flexor and extensor movement of the legs. Haefeli et al. (2011) showed an increased activation over prefrontal areas during the preparation and performance of obstacle steps with EEG. Recently Sipp et al. (2013) showed that walking on a balance beam elicited increased electroencephalographic theta band activity over a wide range of mostly midline cortical areas compared to steady state treadmill walking. Several fNIRS studies have investigated motor preparation during gait. Increased activity over the prefrontal cortex (PFC) and the SMA was observed during adaptive walking compared to steady state walking (Suzuki et al., 2004), as well as during the preparation before gait initiation (Suzuki et al., 2008; Koenraadt et al., 2013). Additionally Koenraadt et al. (2013) found increased activation over the PFC during precision stepping. Consequently it seems that adaptive and challenging training paradigms that continually require participants to adjust their gait are necessary to produce motor planning during gait.

In the current study we examined the impact of an interactive VE feedback task on the EEG patterns during robot assisted walking. We compared this to walking with a visual attention task in which the stimuli were unrelated to the movement and mirror feedback where participants were observing their own movements. We chose these control conditions for two different reasons. First, to account for the amount of visual attention that is required by the interactive feedback task. The visual attention task provides visual stimuli unrelated to the movement, while the mirror feedback consists of visual information relevant to the participants' movement. The latter condition should thus activate the mirror neuron system and account for possible activations of this system during VE feedback. Higher cortical activation during VE compared to mirror feedback and the visual attention task should therefore reflect additional motor planning and visuomotor processing required by the interactive feedback. The second reason we chose the mirror feedback as a control conditions is that in automated gait rehabilitation therapy mirror feedback is often used. Research has demonstrated that mirror feedback during therapy can improve motor recovery after stroke (for a review see Ramachandran and Altschuler, 2009). These studies assume that part of the efficacy of mirror feedback could be due to the stimulation of dormant "mirror neurons." Thus we wanted to examine whether the interactive VE feedback would produce a measurable higher activation of sensorimotor areas relative to mirror feedback.

In particular we hypothesize that walking with interactive feedback in a VE would increase motor planning and intention and thus activate premotor and parietal areas relative to walking with mirror feedback and a visual attention task. Additionally we hypothesize that if the VE task would yield higher cortical activation of these areas compared to mirror feedback interactive VE feedback may be more beneficial for motor learning.

2. MATERIALS AND METHODS

2.1. PARTICIPANTS

Eleven healthy volunteers (26 ± 2 years, 7 male) with no past or current neurological or locomotor deficits participated in this study. The experimental procedures were approved by the ethical committee of the Medical University Graz. Written informed consent was obtained from all subjects before the experiment.

2.2. EXPERIMENTAL DESIGN AND PROCEDURE

Participants walked with a robotic gait orthosis (Lokomat, Hocoma AG, Switzerland) under five different visual feedback conditions. Each condition lasted 4 min and was repeated two times during the experiment. The Lokomat is a robotic driven gait orthosis that includes electrical drives in knee and hip joints and incorporates a motorized treadmill and body weight support system. Parameters of the Lokomat were adjusted according to the common practice in clinical therapy with the help of experienced physical therapists. Walking speed was adjusted according to the participants leg length with the formula: speed $= 0.54(\text{leg})/27.8$ where leg is the participant's leg length in cm and the speed is

computed in kilometer per hour. Walking speed ranged from 1.8 to 2.2 km per hour between participants. For comparison, fast overground walking speed lies at around 5 km/h (Bohannon, 1997). Body weight support (BWS) was adjusted for each participant at around 30%. The Lokomat was run in a control mode with 100% guidance force. The feedback conditions consisted of:

NoFB Participants walked while looking at a black screen.

GAZE Participants looked at white graphical objects sequentially appearing (for 3 s) in different locations on a black screen (see **Figure 1**).

MIRROR Participants watched themselves in a mirror while walking in the orthosis.

3rdP VE and 1stP VE Participants walked in a 3D Virtual Environment in 3rd and 1st person view. The task consisted in steering an avatar down an alley without crashing into the walls marking the edge of the path. The movement of the avatar was controlled using the participant's kinematic information measured within the gait orthosis. Steering of the avatar depends on the force executed by the participant on the gait orthosis and is measured by force sensors within the Lokomat. We used the augmented performance feedback that is implemented as standard in the Lokomat (Hocoma AG, Switzerland).

One gait cycle was defined as the interval between two right leg heel contacts (one gait cycle lasted from 1.6 to 2.4 s depending on the participant's leg length). Before starting the experimental sessions subjects were asked to train under the virtual reality feedback conditions for some minutes to get used to the orthosis and to steering in the VE. After a short training period (about 3 min for each VE task), all subjects reported that they were able to control sufficiently well the VR. Conditions were randomized. In all conditions, participants were asked to look straight ahead, not to close their eyes for prolonged periods of time, and to blink normally. **Figure 1** summarizes the experimental setup.

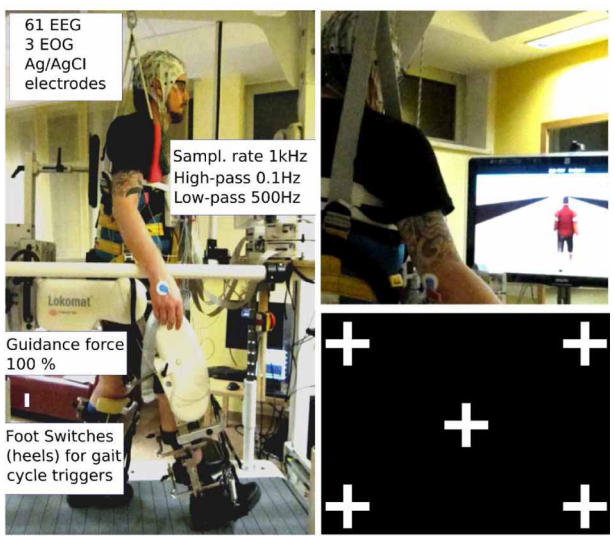

FIGURE 1 | Experimental setup: subject walking in the lokomat gait orthosis with body weight support. The amplifiers for EEG recordings are fixed on a board in front of the participant. The orthosis is adapted and fixed to the participant's legs with the help of an experienced physical therapist; Left: robotic assisted walking. Speed (≤2.2 km/h) and body weight support (∼30%) were adjusted for each participant; Right top: participant walking in the 3rd person VE condition. Right bottom: gaze screen with possible locations for the graphical objects.

2.3. DATA ACQUISITION

The EEG was recorded from 61 sites using two 32-channel amplifiers (BrainAmp MR plus amplifiers, Brainproducts, Munich, Germany). Electrodes were mounted in an electrode cap (EasyCap, Germany) according to the 5% 10/20 system (Oostenveld and Praamstra, 2001). The electrooculagram (EOG) was recorded from three electrodes, two placed on the outer canthi of the eyes and one between the eyes on the forehead. Both EEG and EOG were referenced to the left mastoid, and ground was placed on the right mastoid. All electrode impedances were reduced below 10 kΩ before the recording. Three-dimensional electrode coordinates were measured on a screening day prior to the actual measurement with the Zebris Elpos system (Noraxon, USA). EEG and EOG was acquired with 1 kHz sampling rate, and band pass filtered between 0.1 and 500 Hz. The timing of the heel-strike of both legs was assessed using mechanical foot switches placed over the calcaneus bone at the foot sole of both feet.

2.4. EEG ANALYSIS

EEG data analysis was performed using Matlab 2012b (The MathWorks Inc., Natick, MA) and EEGLAB 11.0b functions (Delorme and Makeig, 2004).

In Wagner et al. (2012) we showed that it is possible to account for artifact contamination of the EEG with Infomax Independent Component Analysis during robotic gait training following the methods of Onton et al. (2006) and Gwin et al. (2010). Before submitting the EEG to an ICA the data was preprocessed accordingly.

First the data (EOG and EEG) were high pass filtered at 1 Hz using a zerophase FIR filter (order 7500) to minimize drifts, low pass filtered at 200 Hz (zerophase FIR filter order 36), and subsequently downsampled to 500 Hz. Channels with prominent artefacts were excluded from further analysis (avg. 2.2; range: 0–7), and the EEG and EOG were rereferenced to a common average reference that was computed from the remaining EEG channels. The continuous EEG data were then visually inspected for non-stereotyped artifacts (e.g., swallowing, electrode cable movements, etc.) and affected partitions were removed from further analysis. For automatic artifact rejection the data were partitioned into segments of 0.5 s to identify outliers exceeding the average of the probability distribution of values across the data segments by ±5 *SD*. On average, per condition 72% of the gait cycles of each participant's EEG data remained in the analysis (range: 61–89%, *SD*: 11).

Next, the preprocessed datasets containing EEG and EOG were decomposed using an adaptive independent component analysis (ICA) mixture model algorithm (AMICA) (Palmer et al., 2006, 2008). AMICA is a generalization of the Infomax algorithm (Bell and Sejnowski, 1995; Makeig et al., 1996) and multiple mixture

(Lee et al., 1999; Lewicki and Sejnowski, 2000) ICA approaches. Infomax ICA utilizes temporal independence to perform blind source separation (Makeig et al., 1996). ICA was performed on individual subjects over all conditions (GAZE, MIRROR, 1stP VE, 3rdP VE, noFB).

Individual component scalp maps were submitted to a single dipole source localization algorithm using a standardized three-shell boundary element head model (BEM) implemented in EEGLAB (Oostenveld and Oostendorp, 2002; Delorme et al., 2012). Individual participants' electrode positions were co-registered and aligned with a standard brain model (Montreal Neurological Institute, MNI, Quebec, Canada). Ideally independent components representing synchronous activity within a cortical domain are characterized by scalp maps fitting the projection of a single equivalent current dipole. Therefore, the goodness of fit for modeling each independent component scalp map with a single equivalent current dipole was used to quantify component quality. Only ICs whose dipoles were located within the head and fitted their scalp projection with a residual variance of less than 10% were considered further.

ICs representing artifacts were identified and rejected from further analysis by visual inspection considering the scalp map, the event-locked time course and the power spectrum. The remaining ICs were submitted to an automatic clustering routine implemented in EEGLAB (Delorme and Makeig, 2004) using principal component analysis (PCA). Feature vectors coding differences between ICs in dipole location, power spectral density (PSD) (3–40 Hz), and scalp projection were reduced to 10 principal components and clustered with k-means (with $k = 13$). Components further than three standard deviations from the obtained cluster centers were moved to a separate "Outlier" cluster. Only clusters that contained more than half of the participants were further analyzed. Furthermore, as we were interested in motor related functions, we considered only clusters in sensorimotor areas.

2.5. CLUSTERS OF CORTICAL ICs

The PSD (using Welch's Method) and event-related spectral perturbations (ERSP) (Makeig, 1993) were computed for each independent source. To generate gait cycle ERSPs single trial spectograms were computed and timewarped using a linear interpolation function, thus aligning the timepoints for right and left heelstrike over trials. Relative changes in spectral power were obtained by averaging the difference between each single-trial log spectogram and baseline (the mean IC log spectrum over all gait cycles per condition). To visualize significant event-related changes from baseline, deviations from the average gait cycle log spectrum were computed with a bootstrap method (Delorme and Makeig, 2004). This analysis revealed gait cycle related activity in one of the clusters that was significant from baseline (see **Figure 2**). This modulation occurred in a varying frequency band ranging from 23 to 40 Hz between persons. For further statistical analysis an individual band in this frequency range was selected for each participant, considering only frequencies that were significantly different from baseline. Spectral activity in 8–12 Hz alpha and 15–20 Hz beta bands did not differ overtly between subjects. Furthermore the spectra of single subjects did not show multiple peaks in these frequency bands. Therefore the standard bands were used for further analysis.

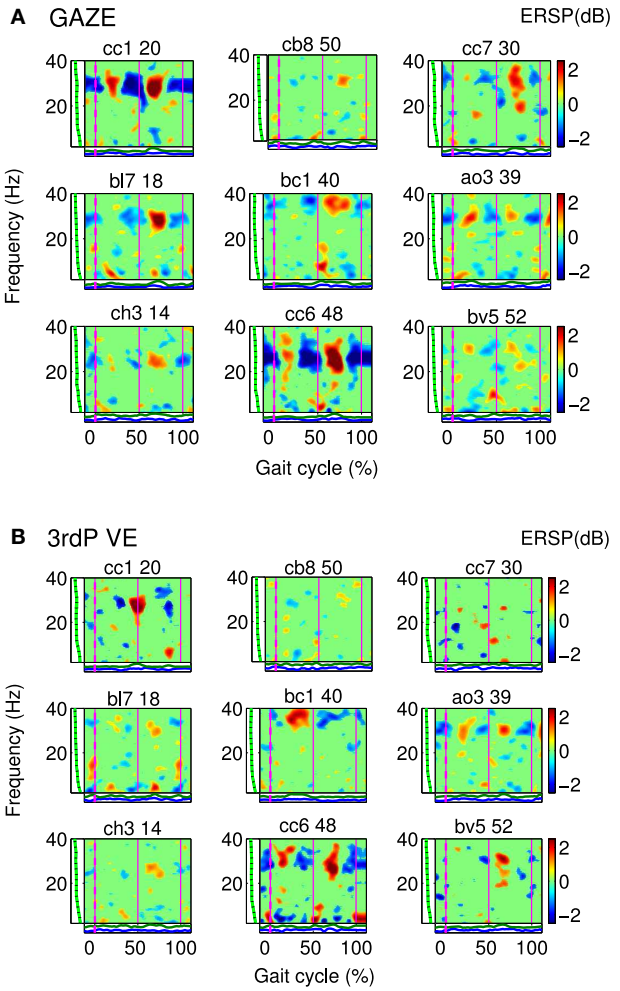

FIGURE 2 | Gait event-related spectral perturbation maps (ERSPs) for cluster A: Single IC plots showing significant changes in spectral power during the gait cycle for (A) GAZE and (B) 3rdP VE. Non-significant differences relative to the full gait cycle baseline ($p \leq 0.05$) are masked in green (0 dB). Vertical lines mark the temporally aligned events of right leg heel contact as the beginning (0%) and end (100%) of the gait cycle, and the left heel-strike (50%). The gait-cycle related modulation in the 23–40 Hz band is more pronounced during GAZE compared to 3rdP VE. The band in which this modulation appears varies over subjects and encompasses frequencies from 23 to 40 Hz. [The codes on top of the figures (e.g., cc1 20) represent participant codes (e.g., cc1), and the number of the IC (e.g., 20)].

For statistical analysis ERSPs were computed for the GAZE, MIRROR, 1stP VE and 3rdP VE using a common baseline: the average gait cycle log spectrum computed from the noFB condition. Independent component ERSPs were then averaged in three frequency bands: 8–12 Hz (alpha), 15–20 Hz (beta), and subject specific bands in the range 23–40 Hz.

For statistical analysis we divided the gait cycle symmetrically in two stationary phases 10–30% and 60–80% of the gait cycle and two transition phases 30–60% and 80–10% of the gait

cycle. Since two of the sensorimotor clusters we identified were located in midline areas we could not attribute their activity to one of the hemispheres (see **Figure 3**). The stationary phases correspond to the midstance (10–30%), initial swing (60–73%), and miswing phases (73–87%). The transition phases correspond to the terminal stance (30–50%), preswing (50–60%), terminal swing (87–100%), and loading response (0–10%) following the definition by Perry (1992).

A repeated measurements 4 × 4 within-subject ANOVA with factors "feedback" (GAZE vs. MIRROR vs. 1stP VE vs. 3rdP VE) and "gait cycle phase" (two stationary phases and two transition phases) was computed for each cluster and each frequency band separately. Multiple comparisons were corrected controlling for false discovery rate (Benjamini and Yekutieli, 2001) with a significance level set *a priori* at 0.05. In cases where the assumption of sphericity was violated significance values were Greenhouse-Geisser corrected. Additionally we computed the effect size η^2. Simple paired *t*-tests with a bootstrapping method were employed for *post hoc* testing, and multiple comparisons were corrected controlling for false discovery rate with an *a priori* alpha level at 0.05. For *post hoc* comparisons we also computed the effect size (cohen's *d*) based on the distance between means.

3. RESULTS

Three clusters located in central midline areas revealed differences between the feedback conditions (see **Figure 3**). The number of subjects and sources contained in each cluster and Tailarach coordinates of cluster centroids are displayed in **Table 1**.

Cluster A, located in the premotor cortex, showed significant changes ($p \leq 0.05$) from baseline relative to the phases of the gait cycle in the band 23–40 Hz visible in the single IC ERSPs during GAZE, NoFB, MIRROR and in reduced form during 1stP VE and 3rdP VE, (see **Figure 2**). This cluster also presented a significant difference in the average spectrum between the feedback

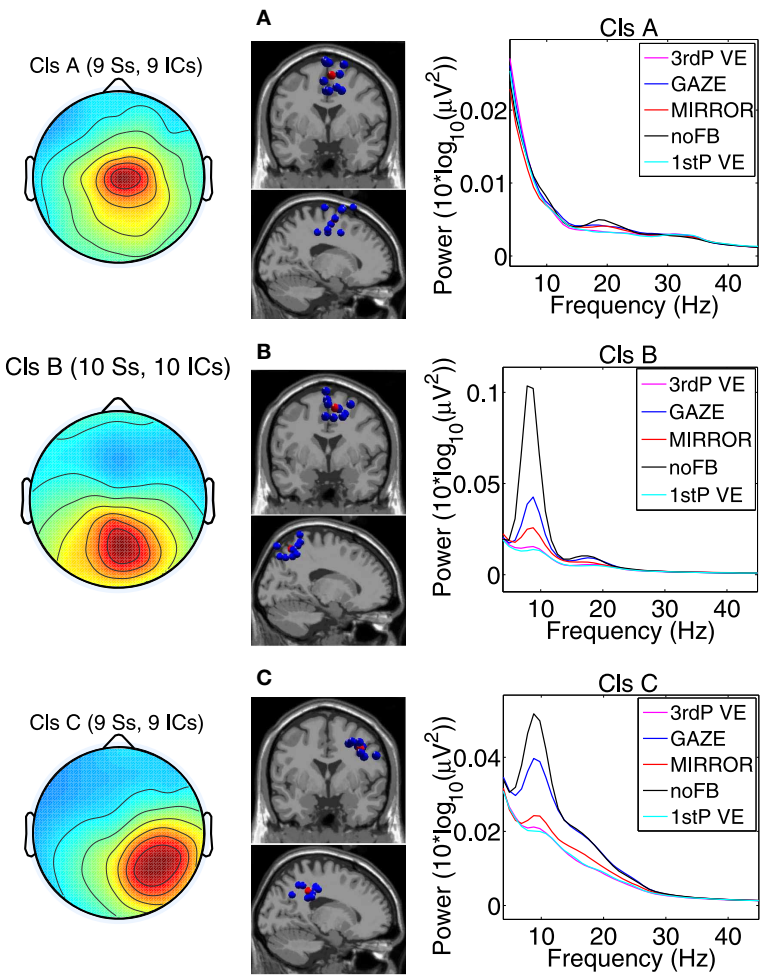

FIGURE 3 | Scalp projection, spatial location and power spectra of independent component clusters (A) Cluster A located in the supplementary motor area (premotor cortex); (B) Cluster B located in the posterior cortex (Brodmann area 7); (C) Cluster C located in the posterior cortex (Brodmann area 40). From left to right in each row: cluster average scalp projections; dipole locations of cluster ICs (blue spheres) and cluster centroids (red spheres) visualized in the MNI brain volume in coronal and sagittal views; PSD for all feedback conditions. For cluster B and C a clear difference in PSD between noFB and Gaze vs. both of the VE conditions in the mu and in the beta range can be observed [Naming: Ss, ICs—number of subjects (Ss) and Independent Components (ICs) in the cluster].

conditions in the beta band ($F_{(3,\ 24)} = 6.9$ $p \leq 0.0094$, $\eta^2 = 0.46$), (see **Table 2**). *Post hoc* tests revealed a significant ($p \leq 0.03$) difference between VE and all other feedback conditions. For gait cycle related modulations in the 23–40 Hz frequency range a significant interaction between gait phases and conditions was found ($F_{(9,\ 72)} = 2.6, p \leq 0.0094, \eta^2 = 0.25$)(see **Table 3**). *Post hoc* tests revealed that power in this range was significantly ($p \leq 0.0085$) reduced in the two stationary gait phases during both of the VE conditions compared to GAZE (see **Figure 4**). But only the second stationary gait phase during 3rdP VE was significantly ($p \leq 0.0085$) different from MIRROR. Compared to GAZE, MIRROR showed significantly ($p \leq 0.0085$) reduced power in this band in the first stationary gait phase. Interestingly there is a significant difference between 1stP VE and 3rdP VE in the second transition phase of the gait cycle. For an overview and Cohen's *d* values see **Table 4**.

For cluster B (parietal cortex, Brodman area 7) the ANOVA revealed a significant main effect for the mean spectrum between the visual feedback conditions in the mu band ($F_{(3,\ 27)} = 9.9$, $p \leq 0.0094$, $\eta^2 = 0.56$), and in the beta band ($F_{(3,\ 27)} = 11.8$, $p \leq 0.0094$, $\eta^2 = 0.60$). *Post hoc* tests show that spectral power in the mu band ($p \leq 0.0025$) and in the beta band ($p \leq 0.0045$) is significantly reduced in the VE conditions compared to MIRROR and GAZE. The ANOVA for cluster C (parietal cortex, Brodmann area 40) revealed a significant main effect for the mean spectrum between the visual feedback conditions for the mu band($F_{(3,\ 24)} = 10.0$, $p \leq 0.0094$, $\eta^2 = 0.55$), the beta band ($F_{(3,\ 24)} = 14.0$, $p \leq 0.0094$, $\eta^2 = 0.64$) and the gamma band

Table 1 | Clusters of independent sources obtained with ICA.

Cluster	Location of cluster centroid (Brodmann area)	Tailarach coordinates (x,y,z)	Number of subjects (S) and ICs
A	Supplementary motor area (BA6)	5, −1, 58	9 S, 9 ICs
B	Parietal cortex (BA7)	8, −56, 55	10 S, 10 ICs
C	Parietal cortex (BA40)	37, −35, 37	9 S, 9 ICs

Table 2 | ANOVA results: significant main and interaction effects.

	Cluster A	Cluster B	Cluster C
8–12 Hz		Feedback $F_{(3,\ 27)} = 9.9$ $p \leq 0.0094$, $\eta^2 = 0.56$	Feedback $F_{(3,\ 24)} = 10.0$ $p \leq 0.0094$, $\eta^2 = 0.55$
15–20 Hz	Feedback $F_{(3,\ 24)} = 6.9$ $p \leq 0.0094$, $\eta^2 = 0.46$	Feedback $F_{(3,\ 27)} = 11.7$ $p \leq 0.0094$, $\eta^2 = 0.60$	Feedback $F_{(3,\ 24)} = 14.0$ $p \leq 0.0094$, $\eta^2 = 0.64$
23–40 Hz	Feedback x Gait Phase $F_{(9,\ 72)} = 2.6$ $p \leq 0.0094$, $\eta^2 = 0.25$		Feedback $F_{(3,\ 24)} = 8.3$ $p \leq 0.0094$, $\eta^2 = 0.51$

Table 3 | Significant differences in mean gait cycle spectra between feedback conditions ($p \leq 0.05$ corrected with false discovery rate), and effectsize (cohen's *d*) (*d*1 and *d*3, respectively denote Cohen's *d* values for 1stP VE and 3rdP VE).

	Cluster A	Cluster B	Cluster C
8–12 Hz		VE-GAZE ($d1 = 1.30$, $d3 = 1.44$) VE-MIRROR ($d1 = 1.05$, $d3 = 0.98$)	VE-GAZE ($d1 = 1.48$, $d3 = 1.19$) MIRROR-GAZE ($d = 1.11$)
15–20 Hz	VE-GAZE ($d1 = 1.09$, $d3 = 1.00$) VE-MIRROR ($d1 = 0.76$, $d3 = 0.74$)	VE-GAZE ($d1 = 1.57$, $d3 = 2.51$) VE-MIRROR ($d1 = 0.91$, $d3 = 0.81$)	VE-GAZE ($d1 = 2.11$, $d3 = 1.57$) VE-MIRROR ($d1 = 0.83$, $d3 = 0.69$) MIRROR-GAZE ($d = 1.21$)
23–40 Hz	see **Table 4**		VE-GAZE ($d1 = 1.65$, $d3 = 1.59$) VE-MIRROR ($d1 = 0.81$, $d3 = 0.64$)

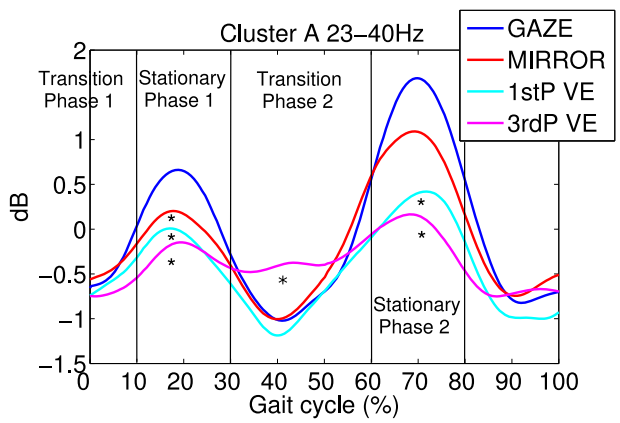

FIGURE 4 | Average gait event-related spectral perturbations (ERSPs) for cluster A: for each feedback condition ERSPs are computed relative to the full gait cycle baseline obtained from the noFB condition. Then ERSPs are averaged over subject specific frequency bands between 23 and 40 HZ and then averaged over subjects for cluster A. Temporally aligned events are marked for the right leg heel contact at 0% as the beginning and 100% as the end of the gait cycle, and for the left heel-strike at 50%. Each feedback condition is represented by a colored trace. It is visible that during 1stP and 3rdP VE in stationary gait phases (10–30% and 60–80%) power in this band is decreased compared to the other feedback conditions. Also a difference between 3rdP VE and 1stP VE during the second transition phase of the gait cycle (30–60%) is evident. Vertical lines mark the beginning and the end of gait cycle phases. Asterisks mark significance between feedback conditions in the indicated gait cycle phase.

Table 4 | Significant differences in single gait phase spectra between feedback conditions ($p \leq 0.0085$) and cohen's *d* values for Cluster A.

	MIRROR	1stP VE	3rdP VE
GAZE	1st stationary gait phase $d = 0.88$	Stationary gait phases $d = 0.63$, $d = 0.95$	Stationary gait phases $d = 0.89$, $d = 1.03$
MIRROR			2nd stationary gait phase $d = 0.65$
3rdP VE		2nd transition gait phase $d = 0.56$	

($F_{(3,\ 24)} = 8.3$, $p \leq 0.0094$, $\eta^2 = 0.51$) (see **Figure 3**). *Post hoc* tests show that spectral power in the mu band ($p \leq 0.0055$) is significantly reduced in the VE conditions and in the MIRROR condition compared to GAZE. The *post hoc* tests also show that spectral power in the beta band ($p \leq 0.013$) and in the 23–40 Hz range ($p \leq 0.0075$) is significantly reduced in the VE conditions compared to MIRROR and GAZE. Additionally the tests reveal that during MIRROR feedback spectral power in the beta band ($p \leq 0.013$) is significantly reduced compared to GAZE. For an overview of significant comparisons and Cohen's values refer to **Tables 2** and **3**.

4. DISCUSSION

Our analysis revealed three independent component clusters in premotor and parietal areas that showed significantly decreased spectral power in alpha, beta and 23–40 Hz frequency ranges during the interactive VE tasks compared to MIRROR and GAZE. This spectral power decrease indicates a higher neuronal activation (Pfurtscheller and Lopes da Silva, 1999).

Gait cycle related modulations in cluster A visible in the single IC ERSPs (see **Figure 2**) showed reduced activity during 3rdP VE compared to GAZE. Statistical analysis revealed that during both VE conditions power in the 23–40 Hz range is significantly decreased in the two stationary gait phases compared to GAZE. Also comparisons between MIRROR vs. GAZE and MIRROR vs. VE show only significant differences in stationary gait phases. Interestingly, however, there is a significant difference between 1stP VE and 3rdP VE in the second transition phase of the gait cycle (see **Figure 4** and **Table 4**). In a previous study we found the same gait cycle related modulation in a 25–40 Hz frequency range during active and passive robot-assisted walking in the premotor cortex (Wagner et al., 2012). Central midline activity in the frequency range 30–45 Hz has been previously related to muscle activation during upper and lower limb movements (Pfurtscheller and Neuper, 1992; Pfurtscheller et al., 1993; Brown, 2000; Mima et al., 2000; Alegre et al., 2003; Müller-Putz et al., 2003, 2007; Raethjen et al., 2008). Results from Pfurtscheller and Lopes da Silva (1999) and Pfurtscheller et al. (1996) suggest that activity in an overlapping frequency band is involved also in motor planning. These studies reported synchrony of oscillations in the frequency range 36–40 Hz over the premotor area and in relation to the sensorimotor area shortly before movement-onset and during execution of movement. Interestingly Petersen et al. (2012) recently observed synchrony in the frequency range 24–40 Hz between EEG recordings over the foot motor area and the electromyogram from the tibialis anterior muscle during steady state walking. The significant coupling occurred prior to heel strike during the swing phase of walking. This corticomuscular coherence is similar in frequency band and cortical location to the gait cycle related modulation we find in the 23–40 Hz range. The stationary gait phases in our study coincide with the swing phases of both legs. Hence the decreased power during VE may represent processes involved in motor planning during these phases. The difference between 1stP VE and 3rdP VE during the second transition phase of the gait cycle is especially interesting and may indicate that participants were using different strategies for steering the avatar in the two conditions. We generally observed a more variable pattern of the 23–40 Hz modulation during 3rdP VE compared to the other conditions.

Our results also show a significant decrease in beta band power in the premotor cortex during VE compared to MIRROR and GAZE. Numerous scalp EEG and ECoG studies have related event-related desynchronization (ERD) in the alpha (8–13 Hz) and beta (15–25 Hz) rhythms to the activation of sensorimotor areas (Crone et al., 1998; Pfurtscheller and Lopes da Silva, 1999; Neuper and Pfurtscheller, 2001; Pfurtscheller et al., 2003; Miller et al., 2007), while synchrony in alpha and beta bands has been connected to a deactivation or inhibition of these areas (Klimesch et al., 2007; Neuper et al., 2007). Interestingly two recent studies showed that elevated synchrony in the sensorimotor beta rhythm promotes postural and tonic contraction and causes movements to be slowed (Gilbertson et al., 2005; Joundi et al., 2012); and a recent review suggests that modulation of beta activity is predictive of potential actions (Jenkinson and Brown, 2011). There is evidence that these principles hold for whole body movements such as walking. Wieser et al. (2010) showed decreased alpha and beta band power during gait like leg movements in an upright position, compared to periods of rest in which participants were lying. Presacco et al. (2011) showed that spectral power in the alpha band is suppressed during precision walking compared to standing. These results are in line with our recent study where we showed that alpha and beta spectral power in sensorimotor areas is suppressed during robot assisted walking compared to standing (Wagner et al., 2012). We also show that spectral power in these bands is significantly decreased during active compared to passive walking. Thus our findings indicate that the task of active gait adjustment in the VE requires enhanced motor planning and increases activity in the premotor cortex. This is in line with numerous studies that relate increased activity in the premotor area to the planning of single limb movements (Pfurtscheller and Berghold, 1989; Ikeda et al., 1992; Tanji, 1994), (for a review see Haggard, 2008). Recent studies have demonstrated that the premotor areas are also activated during gait initiation and adaptation (Suzuki et al., 2004, 2008; Haefeli et al., 2011; Koenraadt et al., 2013).

In the posterior parietal cortex (PPC) two clusters were identified. One located centrally (Cluster B) and one located in the right hemisphere (Cluster C). In Cluster B power in the mu and

beta band was significantly suppressed during both VE conditions compared to MIRROR and GAZE. Cluster C also revealed decreased power in the beta band and the 23–40 Hz range during the VE tasks relative to all other feedback conditions. The 23–40 Hz range is overlapping with the upper beta band, and is suppressed during feedback conditions in which participants had to actively modify their steps. We assume therefore that a decrease in this band has the same functional meaning previously described for the mu and beta band. Alpha and beta rhythms in the parietal cortex have been previously linked to spatial attention, decision making, and sensorimotor integration (Capotosto et al., 2009; Donner and Siegel, 2011; Hipp et al., 2011; Capotosto et al., 2012). Interestingly two recent studies by Tombini et al. (2009) and Perfetti et al. (2011) relate alpha and beta ERD in parietal regions to the movement planning in visually guided upper limb movements under both feedforward and feedback control. For the MIRROR condition a significant power decrease in mu and beta bands relative to the movement unrelated feedback (GAZE) was observed solely in Cluster C. The PPC has been related to the mirror neuron system (Fogassi et al., 2005), we therefore conclude that the activation we find during MIRROR feedback is related to the participants' monitoring of their own movements.

Our results show that parietal cortex regions are more activated in conditions that require visually guided gait adaptation. These results are in line with studies that associate the PPC with visuomotor transformations in reaching movements. Neuronal recordings in monkeys have identified two subareas in the PPC responsible for the action planning of different body parts: the lateral intraparietal area (LIP) for saccades and the parietal reaching region (PRR) for reaching (Snyder et al., 1997). In humans, functional magnetic resonance imaging (fMRI) studies on the PPC have determined regions corresponding to the monkey PRR area (Connolly et al., 2003; Pellijeff et al., 2006). Recently Wang and Makeig (2009) demonstrated that it is possible to decode intended movement direction using human EEG recorded over the parietal cortex with a delayed saccade-or-reach task. Neuronal recordings in cats have revealed a higher activation in the PPC during visually guided gait modification, and suggest that the PPC may contribute to locomotor control (Drew et al., 2008). Interestingly a recent study has related activity in the parietal cortex directly to the awareness of human actions (Desmurget et al., 2009). Previous findings also indicate that the PPC is involved in the planning of eye-movements (Snyder et al., 1997). Planning of eye-movements in our study should have occurred mainly during GAZE as subjects were supposed to direct their gaze to objects appearing in different corners of the screen. In the parietal clusters we can observe decreased power in mu and beta bands during GAZE compared to NoFB (see **Figure 3**). Possibly some of this activity is related to the planning of eye-movements. However, differences between GAZE and VE should reflect the portion of activity not related to saccades.

Our findings that an interactive gait adaptation task activates premotor and parietal areas is especially interesting as these areas have been related to motor intention and motor planning (Haggard, 2008). The increased activity we find in premotor and parietal areas during walking in a VE might thus reflect increased motor planning that is required by the adaptive training paradigm. VE feedback elicited a higher activation compared to movement unrelated feedback and mirror feedback in all of the clusters. Mirror feedback showed enhanced activation relative to movement unrelated feedback only in one of the parietal clusters. This provides evidence that the benefits of gait training with a more demanding and interactive task may be superior to simple mirror feedback.

Interestingly we found a significant difference between 1stP VE and 3rdP VE in the premotor cortex during one of the transition phases of the gait cycle. In general 3rdP VE seems to be related to a more variable pattern of the 23–40 Hz modulation compared to the other conditions, including 1stP VE. This could be an indication that the gait movements are less regular and less automatic involving more motor planing during 3rdP VE compared to 1stP VE, at least during certain phases of the gait cycle. Studies on body ownership show that first person perspective is superior to third person perspective VE for the induction of full-body ownership illusions (Slater et al., 2010; Petkova et al., 2011). These studies relate the first person and third person perspective, respectively to an egocentric and allocentric reference frame. Studies show that the processing of egocentric spatial information and self-motion activates the right parietal cortex (Maguire et al., 1998; Andersen et al., 1999; Vogeley and Fink, 2003). Interestingly in our study we found clusters only in the right parietal cortex, and these were more activated during the VE walking tasks compared to MIRROR and GAZE. However, we did not find differences between 1stP and 3rdP VE in these clusters. Differences between 1st and 3rdP perspective were located in the premotor cortex, a brain region that has been identified in a previous study to be related to the feeling of agency (Tsakiris et al., 2010). From observations we can say that the participants in our experiment needed more time in the beginning to get used to the first person control in the VE. We could speculate that this increased performance success in visuomotor adaptation might have induced a greater feeling of agency in the third person perspective.

Our results further support previous findings (Brütsch et al., 2010, 2011; Schuler et al., 2011) suggesting that a more challenging gait adaptation task can promote the motivation for active participation in the movement. It is, however, not clear to which extent this motivation is increased by the immersiveness of the VE or whether any kind of interactive feedback might have the same effect. A recent study by Zimmerli et al. (2013) suggests that the interactivity of the training environment is fundamental in promoting the participants' active engagement in the motor task. Interactivity can be enhanced by providing functionally significant responses to the movement.

5. CONCLUSION

This study is the first to analyze brain activity during an interactive visual gait adaptation task with a robotic gait orthosis, and to show that the premotor and parietal areas are involved in visually guided gait in humans. We found that mu, beta, and lower gamma rhythms in premotor and parietal cortices are suppressed during conditions that require an adaptation of steps in response to visual input. Such suppression indicates increased activation of these brain areas. We show that this activity is higher compared

to mirror feedback and a visual attention task. Higher cortical activation during visually guided gait adaptation may reflect additional motor planning and visuomotor processing. Activity in the parietal cortex likely reflects direct visuomotor transformations required by the task. Increased activity in the premotor cortex may indicate motor planning involved in adapting the steps to the visual input. Considering studies showing that voluntary drive is crucial for motor learning (Lotze et al., 2003; Kaelin-Lang et al., 2005), our results suggest the possible benefit of goal directed walking tasks that recruit brain areas involved in motor planning. Our results are relevant for gait rehabilitation after stroke and may help to better understand the cortical involvement in human gait control.

ACKNOWLEDGMENTS

This work was partly supported by the European Union research project BETTER (ICT-2009.7.2-247935) and the Land Steiermark project BCI4REHAB. The authors are thankful with Prof. Dr. Peter Grieshofer for providing the Lokomat and Georg Schaffhauser and Pamela Holper for assistance during the experiments. We thank Prof. Ales Holobar and colleagues from the University of Maribor for providing the gaze screen and assistance during the experiments.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 29 November 2013; accepted: 07 February 2014; published online: 25 February 2014.

Citation: Wagner J, Solis-Escalante T, Scherer R, Neuper C and Müller-Putz G (2014) It's how you get there: walking down a virtual alley activates premotor and parietal areas. Front. Hum. Neurosci. ***8****:93. doi: 10.3389/fnhum.2014.00093*

This article was submitted to the journal Frontiers in Human Neuroscience.