Afferent Effects on Brain Computer Interfaces: An Experimental Analysis

Dissertation

zur Erlangung des Grades eines Doktors
der Naturwissenschaften

der Mathematisch-Naturwissenschaftlichen Fakultät
und
der Medizinischen Fakultät
der Eberhard-Karls-Universität Tübingen

vorgelegt
von

Ander Ramos Murguialday
aus San Sebastian, Spanien.

June - 2011

Tag der mündlichen Prüfung: .....13-10-2011.....

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Tübingen, ____18-10-2011_____ _____

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Special thanks to,

I would like to begin these acknowledgements with the most important part of my life, my family, in particular my parents and brother, who always supported me whenever I needed it.

I would like to thank Professor Birbaumer, who gave me the opportunity to work in his lab and whose experience and wise advice were invaluable in guiding me through my thesis and life, also for his excellent supervision of my work and for helping me with lots of paperwork issues.

I need to thank all the people of the Institute of Medical Psychology and Behavioral Neurobiology and specially the ALS and Stroke groups.

I would like to thank Sebastian Halder, Jürgen Mellinger and Jürgen Dax for his help, advice and expertise towards the development of the robotic orthosis, its communication with the BCI2000 module and the set up of the online proprioceptive BCI. During the ALS project an invaluable group of researchers from the Max Planck Biological Cybernetics, the Institute of Medical Psychology and Behavioral Neurobiology, the Neuro Team of the Computer Science Department and the Neurosurgery Department of the University of Tübingen shared frustration, jokes, dinners, meetings, late and very late nights and many working hours.

Specially, my thanks to Femke Nijboer, Michael Bensch, Suzanne Maartens, Jason Faquar and Jeremy Hill. Obviously the project would have not been possible without the advice of Prof. Bernhard Schölkopf, Prof. Alireza Gharabaghi and Prof. Niels Birbaumer and our volunteer GR.

The development and experiments of the proprioceptive BCI would not have been possible without the help and hard work and dedication of Ernesto Soares, Eva Hammer and Silvia Kofler. I must thank all the students, faculty and staff from Professor Birbaumer's lab for their partnership, help and support.

I must thank every person involved as well in the stroke project and the BCCI project for their help, hard work, discussions, advice, partnership, understanding and friendship. I want to thank all of my friends for just being there always (it doesn't matter where).

I greatly appreciate the invaluable support I received from the Fatronik Technological Foundation, now called Tecnalia Research and Innovation, which made possible my stay at the University of Tübingen. They have supported and helped me during this whole process. I want to specially mention Jose Miguel Azkoitia and Thierry Keller, who both believed in my potential and always supported me. This work was supported and funded by the FP7 EU HUMOUR project, the Center of Integrative Neuroscience and by Fatronik-Tecnalia.

I would like to thank the Institute of Medical Psychology and Behavioral Neurobiology and MEG Center, Fatronik-Tecnalia and the Max Planck Training Center of Neuroscience International Max Planck Research School for giving me the opportunity of going to Tübingen to write my PhD.

I want to thank Özge, my wonderful girlfriend for tolerating me through my research work and finally, I want to thank all my family members and friends that are not in this world anymore and have somehow contributed in my development as an individual.

In memory of somebody who wished could have lived and shared this special moment with all of us, my uncle Tomas Murguialday.

Afferent Effects on Brain Computer Interfaces

1. Introduction

A brain-computer-interface (BCI) or brain-machine-interface (BMI) uses brain signals to drive external devices without participation of the spinal and peripheral motor system. BCIs permit action through brain signals such as spike trains from single neurons [Velliste et al., 2008; Riehle & Vaadia, 2005], extracellular local field potentials (LFPs) [Lebedev & Nicolelis, 2006], electrocorticograms (ECoG) [Felton et al., 2007], EEG-Oscillations [Birbaumer & Cohen, 2007], event-related brain potentials (ERPs) [Nijboer et al., in press], real-time-functional Magnetic Resonance Imaging (rt-fMRI) [Caria et al., 2007], and Near-Infrared-Spectroscopy (NIRS) [Sitaram et al., 2007]. In most BCIs the user's brain activity is acquired via amplifiers and filters and decoded using an on-line classification algorithm. In turn, this output is fed back to users, which allows them to modulate their brain activity. The feedback has commonly consisted of sensory stimuli, such as visual [Caria et al., 2007] and auditory [Nijboer et al., 2008a], varying proportionally to the classified brain activity, a discrete reward for a particular brain response, a verbal response (such as "yes" or "no"), the movements of a prosthesis or wheel chair, or direct electrical stimulation of muscles or brain. Thus, feedback of the consequences of the brain activity carried out to control the device is likely an essential part of a successful BCI.

Most of the research devoted to BCI-development consists of methodological studies comparing different on-line mathematical algorithms, ranging from simple linear discriminant analysis (LDA) [Dornhege & Millan, 2007] to non-linear Aritifical Neural Networks (ANNs) [Dornhege & Millan, 2007] or Support Vector Machine (SVM) classification [Lal et al., 2004] and on different spatial or spatio-temporal filtering of the EEG data to achieve better signal to noise ratio [Lemm et al., 2005; Gu et al., 2009]. Single cell spiking for the reconstruction of hand movements requires different statistical solutions [Nicolelis et al., 2004] than EEG-rhythm classification for communication [Nijboer et al., 2008b]. In general, the algorithm for BCI applications are computationally simple and differences in classification accuracy between algorithms used for a particular purpose are small [Hinterberger et al., 2003]. Only a very

limited number of clinical studies with neurological patients are available, most of them single case studies [Birbaumer et al., 1999].

The clinical target populations for BCI-treatment consist primarily of patients with amyotrophic lateral sclerosis (ALS) and severe CNS damage including spinal cord injuries and stroke resulting in substantial deficits in communication and motor function.

1.1. Communication with locked-in syndrome (LIS)

Patients with progressive motor neuron disease, particular amyotrophic lateral sclerosis (ALS), Guillain-Barré-Syndrome and subcortical stroke, as well as patients with traumatic brain damage in vegetative state [Kotchoubey, 2005] may suffer from LIS or complete locked-in syndrome (CLIS). LIS is defined as complete paralysis with one or a few voluntary functions left (usually small eye movements). CLIS consists of complete cessation of volitional control of all voluntary somatic-motor functions. LIS shows intact auditory and tactile perception and intact cognitive functions, usually measured with event-related brain potentials (ERP, [Kotchoubey, 2005]) or fMRI [Owen et al., 2006]. Visual perception is also frequently compromised through paralysis of eye muscles. Therefore, BCIs using the auditory or tactile modality is thought to be the only feedback to be used in CLIS patients.

Since the first report [Birbaumer et al., 1999] of two LIS patients with ALS selecting letters from computer-presented letter strings using learned voluntary decrease of slow cortical potentials, several papers with small samples of ALS patients have appeared that demonstrate BCI controlled communication in LIS and advanced stages of ALS. In a thorough review of the literature it was proposed that BCIs using P300 ERPs [Sellers & Donchin, 2006], slow cortical potentials (SCPs) [Birbaumer et al., 1999] and sensory motor rhythm (SMR)-control [Pfurtscheller et al., 2005] could provide slow but effective verbal communication in all stages of ALS, except the CLIS. Only one study [Naito et al., 2007] reported more optimistic results from a NIRS based BCI in 17 patients with CLIS. Patients were trained to respond with an increase in blood oxygenation (“yes”) or decrease in oxygenation (“no”) to various questions displayed on a computer screen. Using an elaborate off-line classification method, a separation of “yes” and “no” of 70% correct was reported in 7 out of 17 patients with CLIS. One weakness of this study is the relative lack of quantization and definition of clinical criterions used for the CLIS patients. It remains to be determined whether BCIs using EEG, ECoG or NIRS allow voluntary brain responses and communication in CLIS. One possible explanation for the failure to replicate operant control of autonomic functions in the curarized rat [Miller, 1969; Dworkin & Miller, 1986] and for the

lack of learned brain regulation with BCI in CLIS is that goal directed and voluntary thought processes may over time extinguish in the absence of reinforcement contingencies, a hypothesis worthwhile testing in the future [Birbaumer & Cohen, 2007]. If this hypothesis is true a transfer of training success with a BCI from the LIS to the CLIS should be possible. Recently, we were able to decode motor imagery of movements of different speed with successful results in ALS patients providing motor imagery based BCIs for communication with a natural extra dimension which could be used to improve flexibility and training involvement [Gu et al., 2009]. These factors are essential in the transferring BCI control from LIS to CLIS. In this respect we performed an interesting work and tested on ALS patients (Ramos Murguialday et al. 2011). A telepresence platform allowed ALS patients in Germany to remotely control a robot located in Spain. The orientation of the camera attached to the robot and its movements were controlled. Furthermore, an interactive mode was implemented and the ALS patients were able to have a conversation with the researchers around the robot in Spain [Escolano et al., 2010].

1.2. Movement restoration in stroke and spinal cord injury

Several rehabilitative treatments have been used to restore upper and lower limb motor functions. These approaches range from passive facilitation, promotion of alternative movements [Krakauer, 2006], aerobic exercises [Saunders et al., 2009], constraint-induced movement therapy [Sirtori et al., 2009], intense task-directed training, treadmill training [Saunders et al., 2009], bilateral arm training [van Delden et al., 2009], other strategies based on neurophysiological learning mechanisms to promote neuroplasticity such as robot-assisted therapy [Lo et al., 2010], reinforced feedback exercises in a virtual environment (RFVE) [Piron et al., 2010], and recently brain-computer interface (BCI) [Birbaumer & Cohen 2007; Caria et al., in press; Birbaumer, 2006b; Dimyan & Cohen, 2011, Silvoni et al. 2011].

One of the most promising research avenues involves developing neuroprosthetic devices and BCI technologies to bypass brain damage via adaptive neuroplasticity of distant brain areas. Parts of the nervous system not dedicated to a specific task can be harnessed to reconstruct the neural substrate that interacts with the neuro-prosthesis or BCI-driven devices.

In 2003, Pfurtscheller et al. (2003a) reported a tetraplegic patient who, after extensive training to increase and decrease central mu-rhythms was able to control an electrostimulation device (FES)

applied to hand muscles. The patient was able to grasp a glass and bring it to his mouth after he had learned with feedback and reward over a period of 4 months to regulate his mu-rhythm. Hochberg et al. (2006) implanted a 96-microelectrode array into the hand region of the motor cortex of another tetraplegic patient. The patient learned to open and close a prosthetic hand distant from his own hand with intention-driven neuronal ensemble activity. No improvements in voluntary motor function in the paralyzed hand were reported.

Motor disability resulting from chronic stroke represents the main cause of long-term disability among adults and has substantial social, financial and psychological impact on patients, families and society. Approximately one third of all stroke patients are not able to use the paralyzed hand for activities of daily living one year after the stroke. No treatment is available for that condition. A recent study [Buch et al., 2008] using a neuromagnetic BCI showed as a proof-of-principle successful BCI control of opening and closing grasping functions of an orthosis attached to the plegic hand in 6 out of 8 patients. The orthosis was controlled by activity in three of the 275 MEG sensors. Increase of 9-12 Hz mu-rhythm in these 3 sensors opened the hand while decrease closed it. In 6 of the 8 patients mu activity was derived from central ipsilesional location close to the subcortical lesion. After 13 to 22 one-hour training sessions, patients were able to control hand opening-closing functions through the orthosis, in the absence of clinical improvements in the completely paralyzed hands. Training resulted in refocusing of MEG activity, providing first evidence that BCI training may result in well defined cortical reorganization. Whether an invasive BCI with implanted electrodes and internalized connection to the peripheral nerves, or non-invasive BCIs connected to prosthetic devices or rehabilitation robots may move from these “bench” type of study to the clinic awaits further research including different imaging techniques that could help us understand the necessary plastic changes that have to be induced in order to induce functional recovery. Recently, we used a multimodal neuroimaging approach on a single case of partial recovery after stroke and its associated brain reorganization in a chronic patient after combined brain computer interface (BCI) training and physiotherapy. We used fMRI and diffusion tensor imaging (DTI) to investigate plasticity of the brain motor system together with longitudinal clinical assessments finding a convergent association between functional and structural data in the ipsilesional premotor areas [Caria et al.].

1.3. Main strategies in BCIs for restoration

The first strategy is the use of assistive or substitutive strategies, which are technologies and modalities used to bypass an interrupted neural pathway or connection. No direct and specific motor function recovery is promoted explicitly because the cortical activity is used only to mediate and operate an exogenous device [Pfurtscheller et al., 2003a; Hochberg et al., 2006; Müller-Putz & Pfurtscheller, 2008; Gollee et al., 2010; Tavella et al., 2010]. In these cases BCI technology elicits limb movement or/and muscular activation by means of neuroprostheses [Hochberg et al., 2006] or functional electrical stimulation devices [Pfurtscheller et al., 2003a; Gollee et al., 2010; Tavella et al., 2010] or robotic control [Müller-Putz & Pfurtscheller, 2008] to perform daily living tasks. Although no direct motor re-learning is encouraged explicitly, this strategy provides a neuro-feedback learning process to modulate the specific cortical activity in one or more brain areas. This may be one of the few alternatives possible in case of permanent injury, such as spinal cord lesions.

The second strategy uses a classical conditioning approach, attempting to promote neuroplasticity and consequently motor functional recovery. It is based on the contingency of coupling a conditioned stimulus and an unconditioned stimulus attached to a response in a Hebbian manner to produce neural plasticity [Hebb, 1949].

In the specific scenario using the in this thesis developed online haptic-BCI on a stroke survivor, a lesion of the corticospinal tract disconnects a cortical neuron from a spinal neuron. In this case the ERD can be defined as conditioned stimulus (CS1) and the robot-mediated movement (orthosis guided movement) as unconditioned response (UR). The proprioceptive activation of the cortical motor neuron would be a second conditioned stimulus (CS2). The conditioning procedure can be described as follows: repeatedly associating the ERD (CS1) to the robot-mediated movement (UR), causing a proprioceptive stimulus (CS2). The aim of this classical conditioning would be obtaining a voluntary movement or at least muscle activation (Conditioned Response, CR) controlling the ERD (CS1).

Using the SMR based haptic-BCI we would promote contingency between cortical neural activation (the ERD of the movement intention) and the spinal, subcortical or distal neuron activation (proprioceptive re-afferent perception of the movement induced by the orthosis). One can hypothesize that such contingency could facilitate a new activation of a silent connection between these two neurons (cortical and subcortical) and consequently motor functional recovery [Hebb, 1949]. Moreover, it has

been proved that motor function improvement can be induced even in presence of a moderate BCI classification performance [Prasad et al., 2010].

The third strategy uses operant instrumental conditioning, promoting neuroplasticity relying on the contingency of coupling a response and a reward-feedback. In case of a brain lesion which causes the inactivation of a cortical area the BMI would facilitate the activation of an intact perilesional cortical area (sensors for recordings and feedback are placed in perilesional areas). Using my haptic-BCI sytem in which the ERD, a specific task (i.e. opening hand) and a haptic device are integrated, the ERD response is followed by a reinforcing stimulus. The proprioceptive activity induced by the feedback supports the association between the area of the brain generating the ERD with other secondary brain regions. Repeated several times, the contingency might increase the probability of excitation of the perilesional area during the task.

In this scenario the ERD would be the response (R) and the feedback (i.e. robot guided movement) as the reinforcing stimulus (SR). The conditioning procedure would associate repeatedly the ERD (R) to the haptic feedback (SR) obtaining an increased probability of perilesional region excitation, leading to a facilitation of functional recovery.

A similar strategy has been used in the paired associative stimulation (PAS), whereby peripheral and central stimulation coincides to induce spike-timing-dependent plasticity [Bi & Poo, 1998]; PAS has been used to promote motor recovery in patients with stroke showing only electrophysiological effects [Dimyan & Cohen, 2011; Castel-Lacanal et al., 2009].

1.4. Defining afferent pathways for BCI clinical application in neurorehabilitation

The final application of a BCI will determine which type of feedback could suit better the patient clinical status and the neurophysiology involved in each particular clinical picture. In this thesis I focused only on two distinct clinical pictures: Stroke and Amyotrophic Lateral Sclerosis (ALS). For each patient group the neurorehabilitation aim is different. For stroke the goal of the BCI is to induce motor recovery and for ALS to provide the patients with a communication channel.

In this thesis I will describe two different experiments to study the influence of afferent activity on the design and use of BCI systems for clinical use. One experiment was carried out towards stroke rehabilitation using healthy subjects' data and one on a special ALS patient.

In the first experiment the aim was to set up an on-line proprioceptive BCI. Therefore I coupled a SMR based BCI to a robotic hand orthosis enabling on-line control of the orthosis movements in order to study the neural correlates and the influences of the proprioceptive feedback on such motor signals oriented BCI and on the performance using the neuroprosthesis.

The ALS study lasted 8 months in which the patient passed from the locked in state (LIS) to the complete locked in state (CLIS). We studied neurophysiologically the different remaining afferent and efferent pathways in order to enable a communication channel in the CLIS.

2. Studies

2.1. Proprioceptive Feedback in BCI in stroke rehabilitation

It has been widely demonstrated that feedback plays a key role in BCI control learning [Leeb et al., 2006; Barbero & Grosse-Wentrup, 2010] but the question to answer is: what would be the appropriate way to provide feedback to the users in a BCI?

A bar on a screen, spelled characters (P300), cursors and lights [De Vries & Mulder, 2007] are the most used feedback types. Recently vibrotactile feedback [Chatterjee et al., 2007], auditory feedback [Nijboer et al., 2008a] and robot control [Hinterberger et al., 2004] have been implemented. However feedback modality does not appear to be the most important factor concerning the performance using a BCI [Hinterberger et al., 2004].

Stroke survivors with no residual movement of their hands are paralyzed and there are no available rehabilitation therapies for such individuals. BCI systems could be a potential solution for those who suffered a stroke and need to rehabilitate a paralyzed limb and a damaged brain at the same time [Buch et al., 2008; Birbaumer et al., 2008]. On the brain side, some groups performed some motor imagery based therapy improving the motor recovery of the patients [De Vries & Mulder, 2007].

Concerning limb rehabilitation, chronic stroke individuals with a motor impairment get normally passive movement therapy, and recently some research groups have developed new methods using robots as a way of facilitating the therapist work gaining in repetition and movement control in all the rehabilitation sessions [Volpe et al., 2000].

If the goal of the BCI is to bridge the gap between the brain and a motor impaired limb with some afferent pathways intact, such as in a chronic stroke patient, the sensory information to the brain produced by moving the paretic limb will engage motor related areas being used to control the BCI. Since EEG has not very good spatial resolution it is very difficult to discern activity coming from somatosensory cortex, premotor or motor cortex due to the volume conduction effect in which the EGG acquisition is based on. From previous works we know that passive movement influences frequency bands and electrodes in a very similar than active movement or motor imagery [Pfurtscheller et al. 2006]. To date it has not been studied the brain activity resulted from the control of a proprioceptive on-line BCI and the sensory integration and brain processing of the efferent-afferent activity. The synthetic afferent excitation of the brain through the robotic orthosis can produce similar frequency, time and spatial effects than those produced by the motor imagery used to control the BCI therefore biasing in our motor related activity BCI system. The effects could be a reinforcement of the frequency bands on the electrodes used for the BCI control, a non-ending activity loop of activity on those electrodes once the orthosis starts moving the limb, a contrary effect to the one used for the BCI control or an influence to other frequencies, electrodes or time points not influencing the features used for the BCI classifier at all. I studied all these possible effects on the BCI features used and therefore their influence on BCI performance, as well as their neural correlates to define a better filter for afferent and efferent activity towards a better designed biased proofed proprioceptive on-line BCIs.

In this thesis I coupled a mu rhythm based BCI on-line with a robotic hand orthosis to investigate the neural correlates of the system bridging the gap between brain and muscles. I hypothesized that providing online proprioceptive feedback would produce spectral changes similar to the ones used during motor imagery or volitional motor movement based BCIs. If the electrodes and frequency bins used for feedback for a volitional control of the BCI are affected and produced by the feedback, only an initiation of the movement would be needed to maintain an infinite loop of activation without need of voluntary drive. Only adaptation effects or false negatives during the classification would change the classification results. Therefore producing data driven hypothesis to avoid neurophysiological feedback

contamination should be considered and filters designed to assure voluntary control of the BCI without feedback neurophysiological bias.

2.1.1. Experimental Setup

In this work we measured 23 right handed healthy subjects, who were asked to perform 5 different tasks following the randomly presented auditory cues: motor imagery task related to the hand fixed to the orthosis (Class1), driving the orthosis with a hand related motor imagery task (Class2) while receiving fake feedback (unknown to the subject), passive movement provided by the orthosis (Class3), active movement in which the subject opens and closes the hand (Class4) and a rest condition (Class5). All auditory cues were normalized in pitch, length and volume to avoid auditory artefacts during cue presentation. In Class1 and 2 Subjects were asked to perform kinaesthetic motor imagery, i.e. imagine vividly the movements they had to perform, in this case opening and closing the hand. Subjects used a two-state EEG-based BCI to 'control' the hand orthosis during Class2 and upon hearing the corresponding auditory cue, the subject used the appropriate motor imagery task to open and close the prosthetic hand. The subjects were separated in 3 different groups receiving different feedback contingency in Class 2, one getting contingent positive feedback (moving the orthosis with power desynchronization: 9 Subjects), contingent negative (moving the orthosis with power synchronization: 7 Subjects) and sham feedback (the orthosis moved randomly: 7 Subjects). The subjects performed 4 different sessions (different days) completing 5 to 10 runs of 25 trials.

Before starting with the experiment a screening session was performed the first day to identify the best features (electrodes and frequency bins) to be used in the BCI classifier. In this screening session the subjects were randomly presented with visual and auditory cues corresponding to 3 different tasks indicating to either relax (task1), perform kinaesthetic motor imagery of opening and closing the left (task2) or the right (task 3) hand. After a 4 second period performing the tasks a rest cue would be presented indicating to stop. The inter-trial-interval time was randomized between 5 and 7 seconds (See Fig. 1). The subjects underwent 4 runs of 25 trials. The group matching was performed based on the r-square values [Steel & Torrie, 1960] obtained comparing the distribution of data during rest versus right and left motor imagery. The analysis on the screening data was performed using the BCI2000 Off-line analysis module [www.bci2000.org]. The r-square values would indicate the statistical significance of the difference between the two kinds of evoked potentials during the 2 compared tasks.

After this screening session, a cursor control training session and 4 sessions performing the different brain modes was accomplished.

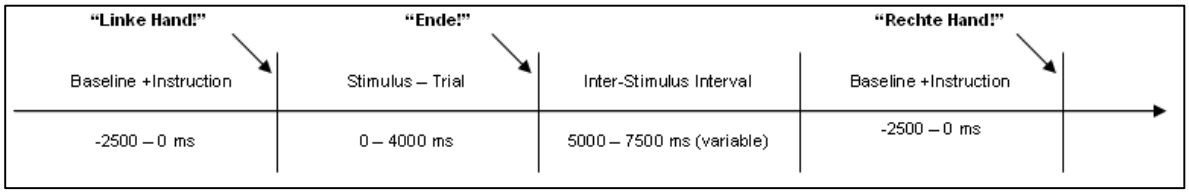

Fig. 1. Timing diagram for the screening session.

For the cursor control training session the healthy subjects were controlling the velocity in the Y axis of a cursor moving from left to right on the screen trying to reach a target presented at the right side of the screen (See Fig. 2). The subjects performed on average 4 runs containing 12 trials reaching all the subjects a target hitting rate of above 70%.

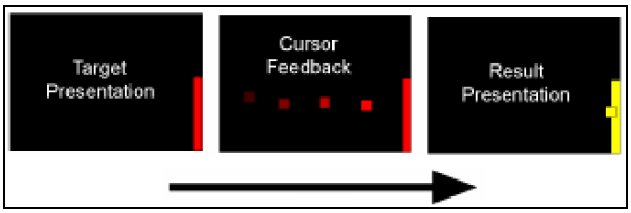

Fig. 2. Cursor control Training.

In the motor modes-submodes sessions the subjects underwent on average 8 runs per session. One run implies 25 trials, 5 for the 5 different randomly presented classes. The subjects were presented with an instruction time in which the brain mode or the "target to reach" were described and after a 2 sec period a "Go" cue indicated the beginning of the 5 sec period of actual trial. The inter-trial-interval was randomized between 7 and 8.5 sec (See Fig. 3). The data was acquired using a high density array of 61 EEG electrodes over the pre-motor, motor and somatosensory cortex, acquiring simultaneously EOG and EMG data for posterior artefact removal.

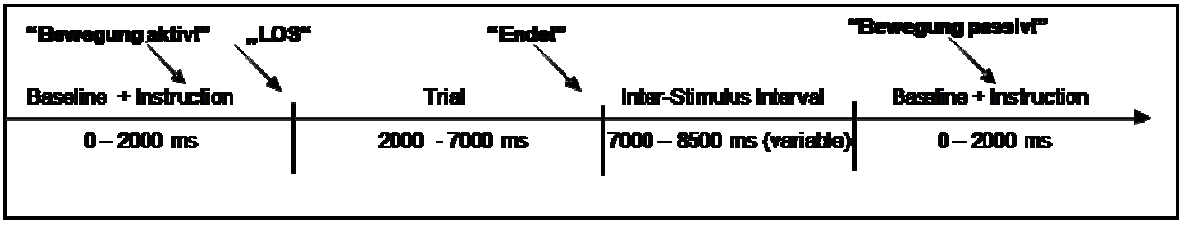

Fig. 3. Timing diagram for the cursor control and brain modes-submodes sessions.

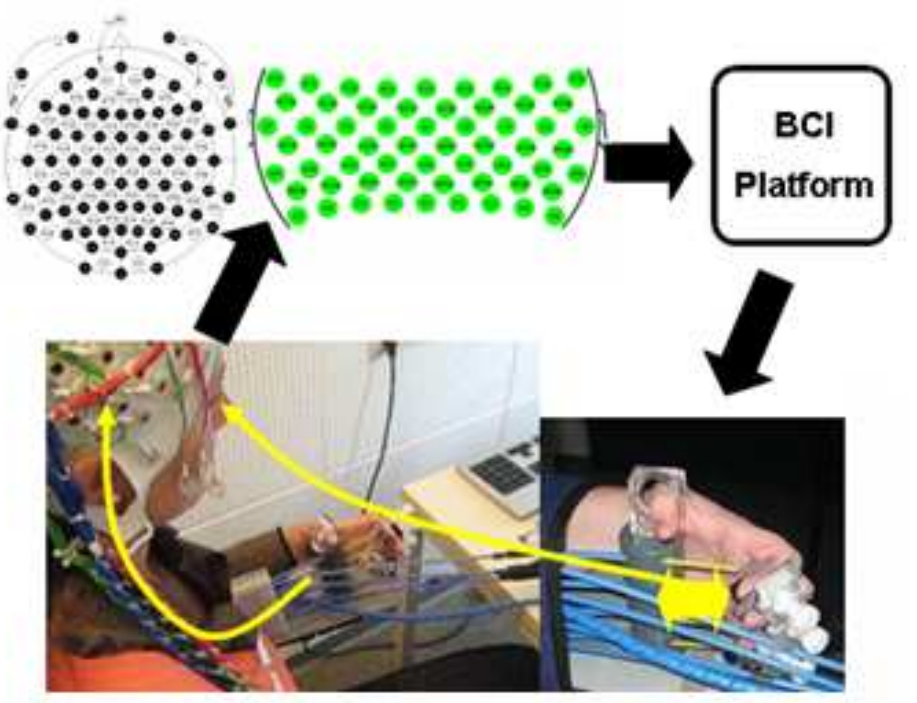

Fig. 4. Proprioceptive BCI setup. 61 Channels from a 128 EEG system were used. The EEG data were analyzed online using BCI2000 and a control signal was produced moving a robotic hand orthosis attached to the users hand providing them with visual and proprioceptive feedback.

2.1.2. Data Acquisition

EEG data were acquired using a BrainAmp 128-channel amplifier from Brainproducts GmbH, Munich Germany. An EasyCap 128-channel EEG cap (modified 10-20 system) from the same company was used for EEG data acquisition; referenced to the nasion, and grounded anteriorly to Fz. 61 channels over the motor areas in both hemispheres were used (See Fig. 4). Additionally, we measured horizontal EOG on both eyes and vertical EOG on the right eye in order to record horizontal eye movements for both eyes and vertical eye movements for the right eye for posterior artefact correction. The Brainamp

amplifier and signal processing module were connected through a client-server architecture, with the amplifier acting as the server and the signal processing module running on a stand-alone client PC. Data were sampled at 500 Hz and transmitted over a TCP/IP protocol to the client PC for storage and real-time signal processing using the BCI2000 platform (www.bci2000.org) [Schalk et al., 2004]). EMG data was acquired using 8 bipolar Ag/AgCl electrodes from Myotronics-Noromed (Tukwila, WA, USA) and placed on antagonistic muscle pairs; one close to the external epicondyle on the extensor digitorum (forearm extensor), other on the flexor carpi radialis (forearm flexor) (See Fig. 5A) other on the external head of the biceps (upper arm flexor) and the last one placed on the external head of the triceps (upper arm extensor). The EMG electrodes impedance was always kept under 20 Ohm.

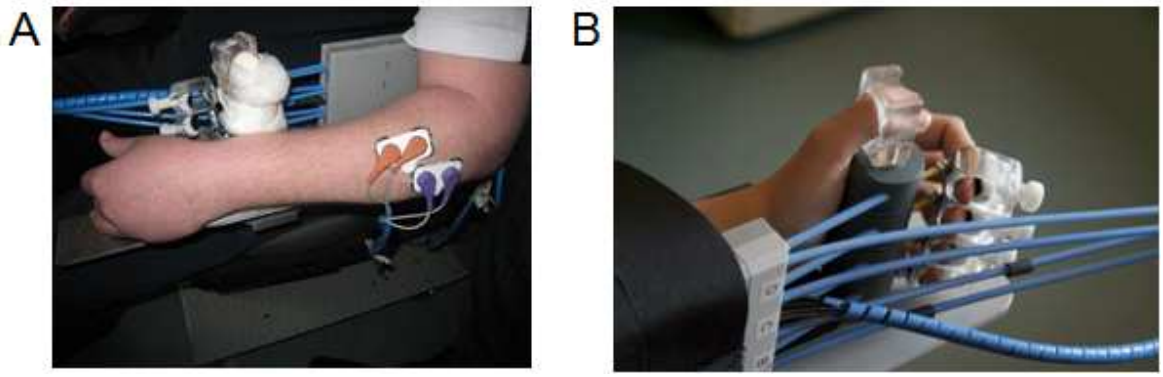

Fig. 5. A) EMG bipolar electrodes fixed to the arm of the subject to control for forearm extension. B) Hand of the subject attached to the orthosis using the individual digit holders.

2.1.3. Orthosis

Each finger was moved individually using a DC−Motor M-28 from Kaehlig Antriebstechnik GmbH, Hannover, Germany with worm gearhead from the same company for each finger. This motor drove via cogwheel and cograil a bowden cable. A finger holder was mounted on the other side of each bowden cable (See Fig. 5B). Near this finger holder an optical position sensor was mounted to detect the finger position independent of the bowden cable tolerance and elasticity. Strain gauges were placed on the Bowden cables near the fingers to detect the finger force in order to regulate the motor force to zero for experiments with active movement trials (the gear motor could not be moved by hand). The power electronics is made as a linear regulation to prevent artefacts from switching devices to the EEG.

The BCI system sent the orthosis positioning and velocity commands and the device transmitted its actual position and velocity state to the host computer upon request. Sending a position command

and a velocity command, will then initiate a movement to the given position with the set velocity. Movement stopped when either the current position was identical to the desired position (as set in the most recent position command), or when the desired velocity was set to zero by the host, in our case the BCI2000 module. The direction of the movement was always determined by the difference between current and desired position defined as the BCI output. As a physical connection between orthosis and host computer, a RS232 serial connection was used at a speed of 38400 bps. The BCI2000 classifier output sent an output every 80 msec and 5 consecutive outputs decoding the same class were needed in order to send the orthosis a no-move (zero velocity value) or a move (positive velocity) command.

2.1.4. Human Robot Interaction Data Analyses

In the complex field of robot-human interaction there are many factors influencing the brain motor mode activated during the therapy. The main brain modes (neural networks excitation) during robotic based motor rehabilitation are related to active and passive motor rehabilitation elicited brain activity. For each of these two main brain modes there are several sub-modes. Within the active mode the influencing factors are on the machine side and the patients could be: assisted, resisted or simply tracked when trying to perform a movement. On the other hand, in the passive mode the influencing factors are on the user side, who can try to perform the movement (although they might not be able to do so), rest or perform motor imagery according to the movement the machine is performing. It is well known that completely passive motor trainings without an active involvement of the patient have not been shown to bring additional gains in motor function, which goes in line with the literature postulating the necessity of active participation and volition in terms of neurorehabilitation and neuroplasticity [Lotze et al., 2003; Hogan et al., 2006; Hu et al., 2009]. Therefore, I aimed at assisted active therapy setting up the first online proprioceptive BCI. In this respect the control signal to move the robot and the feedback contingency perceived by the user are of vital importance to enable neuro-motor-rehabilitation. In this work I based my approach towards motor rehabilitation of stroke survivors. This cerebrovascular accident leads to different levels of impairment and therefore, the active control source signal will directly depend on the remaining muscle control. Force and kinematics sensors are normally used for those stroke survivors who still have a respectable residual movement [Krebs et al., 2007; Takahashi et al., 2008]. Nevertheless, electromyography (EMG) sensors have been used as well as a control signal alone or combined with force or kinematics sensors [Fukuda et al., 1998; Dipietro et al., 2005; Hu et al., 2009]. For the patients that are consider to be paralyzed and have no residual movement

in the affected joints, EMG (if present) and electroencephalography (EEG) signals combined or alone might be the only non-invasive remaining signals that could be used to trigger robot movements and therefore close the loop bridging the gap between brain and end effect (hand movements in this case). By closing the loop we would induce contingent afferent and efferent neural flow linking the intention to move and the sensory inputs moving the patients hand through the robotic hand orthosis. The sensory feedback would be provided visually (observing the hand moving) and haptically (feeling the hand moving) since most of the paralyzed stroke survivors retain some haptic sensation.

In order to design a proper platform for motor rehabilitation of paralyzed stroke survivors, it is of high importance to understand the brain activity present in each brain mode or submode during the specific therapy and therefore understand and design an optimal rehabilitation model. Furthermore, bias related to afferent brain activity need to be studied in order to ensure a pure volitional control of the orthosis when using a BCI and therefore improve rehabilitation outcomes.

All this together, being in the scenario of our proprioceptive BCI system for motor rehabilitation, suggests the need of analyzing different brain activations during the most common motor modes such as passive movement, active movement, motor imagery mode, rest and motor imagery controlling passive movement of the arm (simulating the case of a paralyzed patient trying to move and been assisted by the proprioceptive-BCI-robot).

I hypothesized that:

a) The brain activity during the control of the proprioceptive BCI would resemble the neural activation generated during active movement.

b) I expected to find significant differences between the brain modes in frequency and time that could be used to design filters to separate voluntary intention to move or movement, from proprioceptive brain activation. This could lead to a substantial improvement in the control and assessment of different rehabilitations therapies using motor imagery, passive movements (robotics) and proprioceptive BCIs.

c) I expected to detect significant compensation effects when performing a task with only one side. This would generate the excitation of brain activities not related to the task I wanted to reinforce with the proprioceptive BCI feedback.

d) I expected to observe feedback contingency effects in BCI control producing a learning effect in the contingent groups having a higher performance in the contingent positive group. No learning effects were expected in the sham feedback group.

Using the data acquired in the experiment, several analyses were performed addressing the different open questions regarding the use of proprioceptive BCIs for motor rehabilitation:

1) How much movement compensation, i.e. undesired muscle activation, is happening while using a robotic hand orthosis, regardless if the orthosis is controlled or not using a BCI and how much does the compensation (muscle activity in the ipsilateral resting arm) affect the EEG data used for the BCI. [Ramos Murguialday et al., 2010]

2) Different motor modes and submodes related brain activity influence on the performance of a motor activity related BCI and the differences within and between the three different feedback contingency groups. [Ramos Murguialday et al., 2009; Cho et al. 2011, Ramos Murguialday et al., in preparation] and their correspondent neural correlates (EEG) in the time frequency domain.

2.2. Analysis of movement compensation (EMG bias) in motor neurorehabilitation using BCIs

2.2.1. Upper Limb EMG influences in Motor Imagery based BCIs

In the motor imagery BCI the motor task related EMG artefact rejection has not been a topic of interest. The minimal contraction of muscles related to the motor imagery has not been controlled and its neural correlates have not been analyzed. In the beginning of the mu rhythm-based BCI studies, controlling for EMG activations was completely absent. Most of the groups assumed no muscle activity while performing motor imagery [Fatourechi et al., 2007]. Later, some EMG electrodes were placed on the limbs related to the motor imagery due to small movements produced by the subjects [Wolpaw & McFarland, 2004; Birbaumer, 2006a], commonly used methods for removing EMG artefacts in EEG signals are linear filtering [Barlow, 1984], blind source separation and independent component analysis ICA [Halder et al., 2007], principle component analysis [Lagerlund et al., 1997] and wavelet transforms [Browne & Cutmore, 2002]. An artefact-removal method should be able to remove the artefacts as well

as keep the related neurological phenomenon intact. Therefore, if sufficient data is acquired, trials with artefact presence should be compared to the cleaned data. Furthermore, EMG activity was found in the "resting" forearm extensor muscles during muscle activity tasks involving the opposite forearm and while performing mental task not related to finger movements [Sogaard et al., 2001], similar to Whitham et al. (2007) findings in paralyzed subjects with a single limb paralysis. They suggested that EMG activation during just mental activity may be related to evolutionarily important mechanisms for fight or flight namely mental activity may constitutively activate protective programs of preparedness for action [Whitham et al., 2007; 2008].]. It has been well-documented that motor intentions and motor imagery can be accompanied by occasional, task-related subliminal muscular activity, usually being a small fraction of its real counterpart [Gandevia et al., 1997; Guillot & Collet, 2005; Guillot et al., 2007; Hashimoto & Rothwell, 1999; Jacobson, 1932; Lebon et al., 2008; Shaw, 1938]. Therefore, it is important to note that the requirement without muscular activation is not always met for motor imagery. This is also in line with the so-called ideomotor principle, in which actions are initiated by the anticipation of their consequences (also termed psychoneuromuscular theory: James, 1890; Knuf et al., 2001; A. Stock & C. Stock, 2004; cf. inverse modeling: Wolpert & Gahramani, 2000; Wolpert et al., 2001). The anticipation, i.e., movement intention or motor imagination, can induce weak EMG activation resulting from incomplete inhibition of the efferent motor command [Jeannerod, 2001; Jeannerod & Frak, 1999]. Nevertheless no research group has performed an exhaustive study of the influence of arm muscles contractions on the EEG recorded activity. On the other hand, most of the EMG artefact rejection algorithms in BCI, use very simple features like the root mean square (RMS), variance, or rectified signals [Vuckovic & Sepulveda, 2008; Wolpaw & McFarland, 2004; Birbaumer, 2006a] to detect muscle activity. Furthermore, these methods use a small number of data before the onset of the stimulus to calculate the threshold used for EMG activity onset detection [Vuckovic & Sepulveda, 2008], or the time between trials, or they simply use the EMG activity recorded during the trial to calculate the mentioned threshold. Recently Nikulin et al. (2008) observed that the so called "quasimovements" i.e. muscle contraction not eliciting movement, can elicit similar brain activation than performing motor imagery task. In Nikulin's work subjects were asked to reduce incrementally the muscle contraction until no movement was elicited. Once that level was reached, a mu rhythm-based BCI was utilized to measure the subject's performance after a cue presentation following the "quasimovements" strategy. All this together suggests that the influence of these small muscle contractions while performing motor imagery might have an important relevance in the BCI.

In this analysis we performed EMG correction of the data to detect trials with EMG activity using different rejection methods. We intend to study how the EMG activity and the resulting afferent brain activation of cortical sensorimotor areas could affect the neural activity used in a motor activity based BCI. The activity produced by involuntary muscle contractions will produce afferent activity reaching the cortex eliciting similar activity to one produced by the motor task used to control the BCI i.e. usually motor imagery or motor intention. This could introduce a bias in the BCI if the afferent activity influences the features used for the classification of different brain activities. In this analysis we compare the different traditionally used EMG rejection methods with novel and more precise methods used in EMG activity detection and decoding [Tenore et al., 2009].

2.2.2. Signal Processing

The EMG activity data was highpass filtered at 10 Hz and rectified. We used a 200 msec sliding window with a 180 msec overlap to calculate the following 5 EMG time-domain features: Root Mean Square (RMS), Variance (VAR), Mean Absolute Value (MAV), Wave length (WL), Willison Amplitude (WA). A sixth feature, Rectified Data (RD), was also used, which did not need windowing the data. The MAV displays a large increase in value at onset and maintains fairly high values during muscle contraction. The WL provides indicators for signal amplitude and frequency. WA represents the different muscle contraction levels. The VAR represents the EMG signal power, helping to identify onset and contraction and the RD represents the envelope of the muscle activity and therefore the muscle overall contraction.

1. **Variance:** Starting in late 1970s, the EMG signal was modeled as amplitude modulated Gaussian noise whose variance is related to the force developed by the muscle. The variance (or second-order moment) of the EMG is a measure of its power, and it is given by

$$\mathrm{VAR} = \sigma^2 = \frac{1}{N-1} \sum_{k=1}^{N} x(k)^2$$

   Where N stands for the length of the window in number of data points.

2. **Mean absolute value:** (MAV) Increases in movement speed were accomplished with less averaged rectified EMG (AEMG) and reduced steadiness for eccentric contractions compared with concentric contractions (when a movement occurs, the antagonistic muscles suffer an

eccentric contraction, while the agonistic contract concentrically). MAV is an estimate of the mean absolute value of the signal x_i in a segment i that is N samples in length.

$$MAV = \sum_{k=1}^{L} |x_k| \text{, for i} = 1,..., \text{I - 1}$$

3. **Waveform Length**: (WL) This is a parameter that can estimate the complexity of the EMG waveform. The calculation is defined as

$$\boldsymbol{WL} = \sum_{\boldsymbol{k}=1}^{\boldsymbol{L}} |\Delta \boldsymbol{x_k}| \quad \Delta x_k = x_k - x_{k-1}$$

The waveform length of the signal provides indicators for signal amplitude and frequency.

4. **Willison Amplitude:** (WAMP) This parameter is used to count the number of times that the signal amplitude exceeds a predefined threshold. It is an indicator of firing of unit action potential and therefore an indicator of muscle contraction level. The definition is as

$$WA = \sum_{k=1}^{L} f(|x_k - x_{k+1}|)$$

where $f(x) = 1$ if $x >$ threshold and 0 otherwise

5. Root Mean Square: (RMS) t reflects the physiological activity in the motor unit during contraction

$$\boldsymbol{RMS} = \sqrt{\frac{1}{\boldsymbol{L}} \sum_{\boldsymbol{k}=1}^{\boldsymbol{L}} \boldsymbol{x_k^2}}$$

2.2.3. Artefact Rejection

We performed a whole battery of artefact rejection methods. The rejection methods were based in 3 steps: 1) EMG Feature used, 2) time used as reference consider free of muscle activity (RTh) and 3) electrodes used to detect the EMG activity. The feature extraction was performed using the 6 different

time domain features (RMS, WL, VAR, MAV, WA and RD). In order to determine what is consider being a muscle contraction a threshold based on the mean amplitude off the extracted feature during a reference period of time consider to be free of muscle activity was used. We implemented 3 different methods to calculate the rejection threshold: A) The first rejection threshold (RThA) was determined at 3 standard deviations (SD) of the extracted feature values on the rest class (Class5) in which all the trials were previously cleaned of artefacts rejecting all the trials that had at least one value higher than 2 standard deviations above the mean. B) The second rejection Threshold (RThB) was defined at 3 SD calculated on the motor imagery class (Class1) in which the users were instructed to perfom motor imagery of opening and closing the hand. C) The third rejection threshold (RThC) was calculated at 3 SD during the inter trial interval (ITI) time and D) The last rejection threshold (RThD) was at 3 SD using the instructions period to calculate it, i.e. the 2 seconds the GO cue.

We performed 3 different rejections depending on the electrodes used to detect artefacts rejecting a trial if at least during 250 msec the feature values extracted during the task crossed the pre defined threshold on: a) any of the 8 bipolar electrodes placed on both arms (BOTH), b) any of the 4 bipolar electrodes placed on the arm attached to the orthosis (IPSI) and c) any of the 4 bipolar electrodes placed on the contralateral arm relative to the arm attached to the orthosis (CONTRA). To Class 4 (active movement) only the option c was applied, using just the electrodes placed on the resting arm.

In all, we therefore used 72 EMG activity detection methods (6 features x 4 periods for threshold calculation x 3 different sets of electrodes).

2.2.4. Results

We compared the proportion of trials accepted as EMG activity-free, i.e. without EMG artefacts, relative to the total number of trials using the 72 different detection methods. Overall results, averaging across all session, all subjects and irrespective of the class, are presented in Figure 2. Methods were ordered in ascending proportion of trials classified as EMG activity-free. In the Y axis we have the proportion of trials classified as clean, i.e. no muscle activity detected, being 1 if no trial was detected to be corrupted with EMG and 0 if all trials were detected as corrupted. Subjects displayed significant muscle activity while performing all of the different tasks. Furthermore, different methods have distinct EMG-activity detection sensitivities, consequently rejecting different proportions of trials. On average, the most stringent method, yielding the least number of artefact-free trials, i.e. without artefacts,

located in position 1 in Figure 6, used electrodes from both arms (BOTH), the Rest time period (RThA) for threshold calculation and Feature 5 (WAMP). The least stringent method used electrodes from the ipsilateral arm (IPSI), the inter-trial interval time period (RThC) for threshold calculation and Feature 6 (RD).

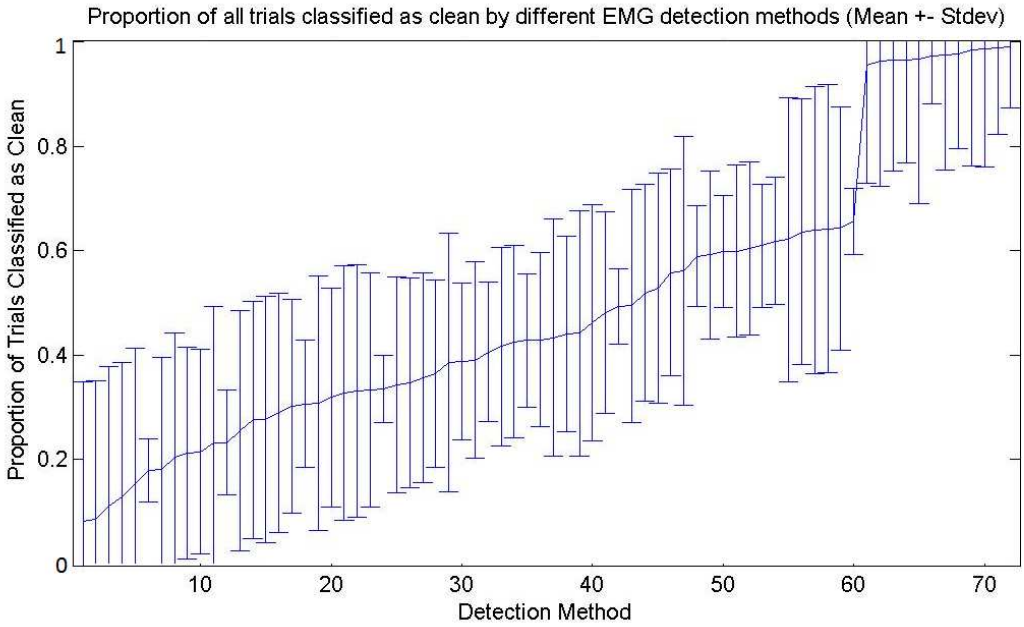

Fig. 6. Average proportion of the total number of trials classified as EMG activity-free using the different detection methods. Error bars depict session-wide standard deviations. The Y axis represents the percentage of trials identified as cleaned without EMG activity after artefact rejection, being 1 if all trials were detected as clean and 0 if all were detected as contaminated. The X axis represent each of the 74 methods used to detect the presence of EMG activity during a trial ordered from most to least sensitive detection method. As we can see there is a significant difference depending which rejection method was used.

In order to evaluate the influence of the 3 steps characterizing each rejection method (*Feature, Time period used to calculate the threshold, Electrode Location*), detection methods were separated for each step, their average performance was calculated across all sessions, subjects and task classes. We generated a figure for every rejection step being the selected step variables (for example: step=features variables=[VAR, MAV, RD, WL, WA, RMAS]) represented by individual lines, the X axis being the different rejection methods obtained by the combination of the remaining rejection steps (*time period used to calculate the threshold* and the *electrode location;* 4RTh x 3Electrode Locations = 12 rejection methods) and Y axis representing the proportion of trials classified as clean, where 1 would mean no trials detected as having EMG activity and 0 would mean all trials detected as contaminated with EMG.

By separating the methods according to the EMG feature used, we evaluated the influence of the different EMG features in EMG activity detection. Results are presented in Figure 3, where for each EMG feature, the trial-wide average proportion of EMG activity-free trials is presented for each of the 12 classification methods (4 thresholds x 3 electrode locations).

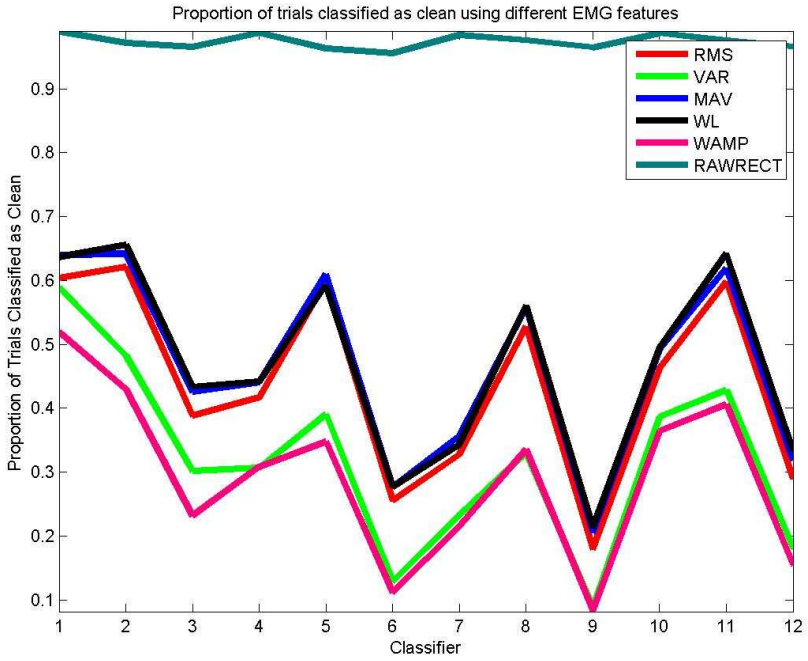

Fig. 7. Average proportion of the total number of trials classified as EMG activity-free using different EMG features. The Y axis representing the proportion of trials classified as clean, where 1 would mean no artefact detetcted and 0 all trials classified as artefacted. The X axis represents the 12 rejection methods using the different intervals for the threshold calculation and electrodes used for the detection. Each coloured line represents the different rejection methods detection rate combining a different time domain EMG feature. RMS stands for root mean square, VAR for variance, MAV for mean absolute value, WL for wave length, WAMP for willison amplitude and RAWRECT for rectified raw EMG data. We can observe that the WAMP and VAR are the most sensitive methods showing almost the same rejecation rate, while RMS, WL and MAV detected 15 to 25 % less artefacts and rectified raw EMG data detected almost no artefacts.

The WAMP feature was observed to be the most stringent, closely followed by VAR. The least number of trials were eliminated using the RD feature showing a very low dependency of the other 2 rejection steps indicating a very low EMG activity detection sensitivity. The peaks in the plot correspond to more or less sensitive methods depending on the other 2 steps of the rejection method (electrodes and time period used to calculate the threshold). Therefore, the influence of the time period used to calculate the threshold was then studied using the same procedure. The session-wide average performance of the 18 different rejection methods (3 electrode locations x 6 features) is presented in Figure 7; where every line depicts a different variable for the *time used to calculate the rejection*

threshold step (Rest, Inter-Stimulus-Interval, motor imagery task, instruction). Using the Rest period (RThA) to calculate the threshold yielded the least number of trials detected as EMG activity free, while using the ITI (RThC) proved to be the less stringent method. These results indicate that during the Rest period subjects displayed the least muscle activity, thus yielding lowest thresholds (RThA) and, therefore, lowest proportion of trials classified as EMG activity-free. The inverse applies to the ITI. As we can observe in Figure 7, 3 different combinations of the other 2 rejection steps (EMG features and electrodes used) produced high peaks indicating that for a certain combination of EMG feature and electrodes the time used for calculating the rejection threshold does not have any influence in the percentage of trials detected with EMG activity thus the sensitivity of the EMG feature-electrodes used couple is already extremely low. The peaks were caused by the combination of the rectified raw data EMG feature with the three different electrodes location proving the low sensitivity to detect EMG activity using rectified raw data. Two rejections step combinations showed an EMG detection rate of 100% of the trials marking all the trials as having EMG activity.

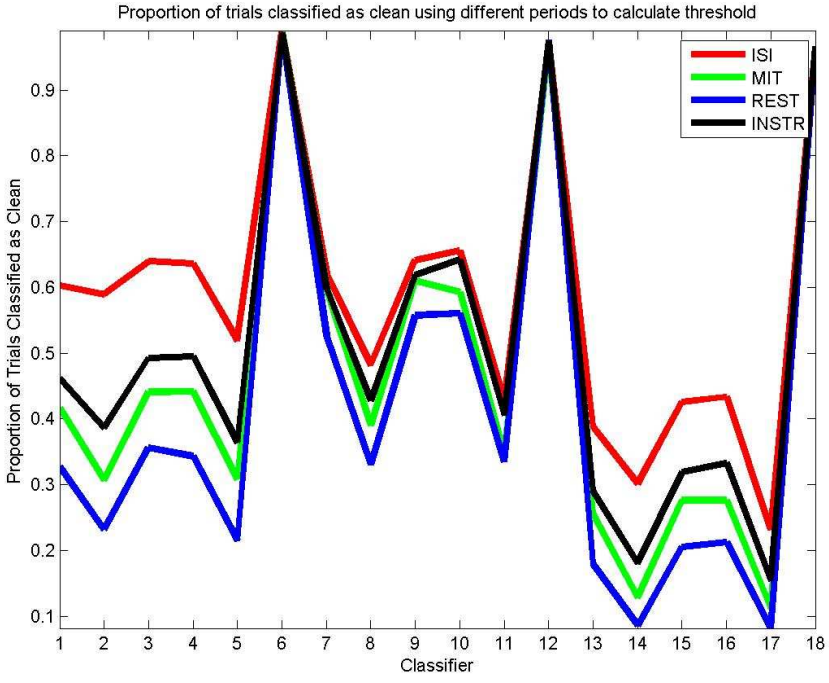

Fig. 8. Average proportion of the total number of trials classified as EMG activity-free using different time periods to calculate the threshold used to detect EMG activity (colour lines). The X axis represents the 18 rejection methods combining the different EMG extracted features and electrodes used for the detection.ISI stays for Inter-Stimulus-Interval, MIT for motor imagery task, REST for resting task and INSTR for the instruction period during the 2 seconds prior to the GO cue. Using the ISI to set up the threshold showed the lower EMG artefact sensitivity for half of the rejection methods followed by the INSTR and MIT and being the REST the time period to calculate the rejection threshold the most strict method. The peaks are due to the use of the

rectified EMG data and the short differences in methods 7 to 11 are due to the EMG features used showing similar artefact detection performance (See Fig. 7).

Finally, we studied the influence of electrode location on the proportion of trials detected as EMG-activity free. The session-wide average performance of the 24 different rejection methods (4 Time periods used to calculate the threshold x 6 features) are presented in Figure 4. As was expected, using electrodes placed in both (BOTH) arms proved the most stringent method, followed by methods using the arm attached to the orthosis (IPSI). Using electrodes on the contralateral arm (CONTRA) yielded the least number of rejected trials. Again the rectified raw EMG data demonstrated insignificant sensitivity to electrodes location showed by the highest 4 peaks on Figure 8. There are 2 methods using all electrodes that classified all trial as EMG contaminated corresponding to the use of the Variance and Willision Amplitude as EMG features and the using the rest time to calculate the rejection threshold.

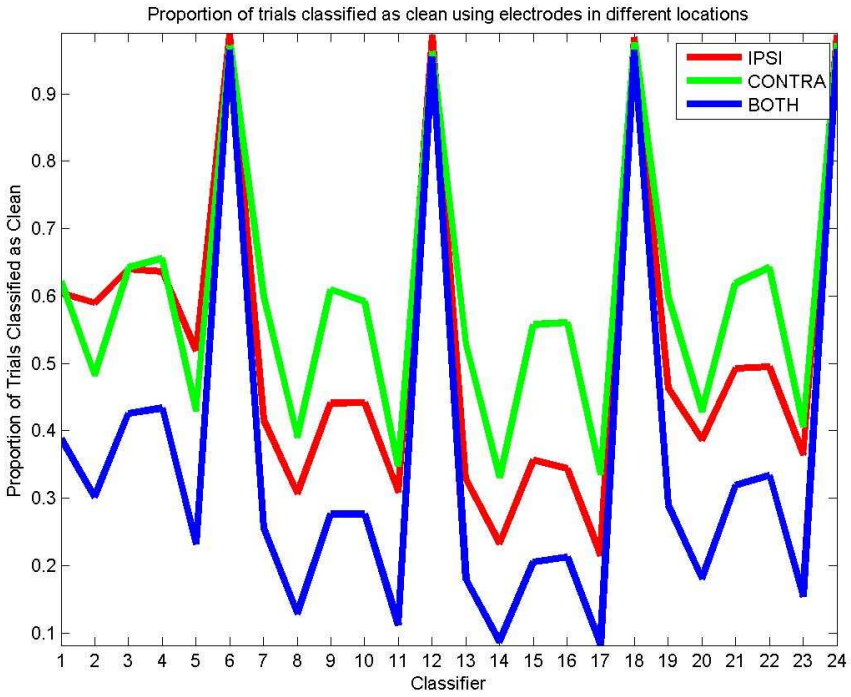

Fig. 9. Average proportion of the total number of trials classified as EMG activity-free using different electrode locations. IPSI stays for electrodes placed in the task related hand (attached to the orthosis), CONTRA for the contralateral and free hand and BOTH for all electrodes placed on both arms. The X axis represents the 24 rejection methods combining the different intervals for the threshold calculation and EMG extracted features. The use of both arms electrodes resulted in more trials detected as presenting EMG activity while the contralateral electrodes resulted in a lower number of trials identified as contaminated with undesired EMG activity. This indicates a higher number of involuntary contractions in the arm attached to the orthosis as expected.

2.2.5. Conclusion

Improperly controlled or filtered EMG activity can elicit neural signals upstream to the brain influencing the commonly used frequency domain for BCI systems. This neural activity could bias the brain signals used for BCI control, when produced, in a scenario in which EMG activity is not desired. For the control of prosthetic devices oriented towards completely paralyzed individuals, has to be noticed that EMG activity in terms of "quasimovements" could influence the neural signals used by the BCI classifier when using healthy subjects as a control for the development of such BCIs. This data suggest that testing the BCI on healthy subjects could lead to false results in terms of accuracy if the "quasimovements" are not wanted or present in that type of BCI application. A significant larger number of trials and a much more control of EMG activity would be needed to study the use of purely motor imagery and not “quasimovements” activity in the development of BCI for completely paralyzed patients using healthy subjects as experimental group or to claim motor imagery based brain control with no muscle contractions in healthy individuals.

A quantification of the potential bias of the BCI system caused by small muscle contractions is needed to determine how to remove or avoid this effect. In this thesis section we demonstrated that many BCI and upper limb motor control studies that did not control for EMG artefacts could be biased by small muscle activity of the limbs and therefore not valid as proof of concept design for completely paralyzed patients.

2.3. Analysis of different motor modes neural correlates and performance

2.3.1. Influences on the performance of a motor activity related BCI and the differences within and between the three different feedback contingency groups

In an active motor related rehabilitation therapy the feedback plays a very important role coupling intention and action. The character of feedback has been distinguished according to four aspects; the mode of feedback (visual, auditory, haptic, etc.), the moment of feedback (continuous or binary) and the transmission of the feedback (contingent or non-contingent). The expression

"continuous" refers to the difference whether feedback can be presented all time during a trial or whether is presented binarily once at the end of each trial. When using a linear classifier, after a threshold/s is defined, feedback is provided each time the brain activation reaches that limit, either during the ongoing trial (continuous), or once at the end of the trial (binary). The distinction between contingent and non-contingent defines the correspondence of the feedback to the strength of activation regarding the EEG component used for feedback. In this thesis case I wanted to develop an online (few milliseconds delay) continuous haptic BCI system to study the difference in brain mode BCI performance and the influence of the feedback contingency on it.

It has been already shown that contingent feedback which continuously reflects the current activation level of the particular brain area constitutes the best adjustment for providing optimal operant conditioning processes. This idea also goes in line with the model of motor skills according to which physiological functions can be better trained the more re-afferent information returns [Travis et al., 1974; Kisil & Birbaumer, 1992]. On the other hand, whether feedback is indeed essential for training the self-regulation of neurophysiological parameters or not has not yet found an answer. Furthermore, while some studies demonstrate success in self-regulating physiological parameters even without feedback [Bouchard & Granger, 1977; Young & Blanchard, 1974; Cuthbert et al., 1981], others demonstrate the necessity of feedback for initially learning to use this mental strategy [DeCharms et al., 2004].

Different motor related brain modes and submodes like active movement, passive movement and motor imagery have been studied using EEG and some of their neural correlates presented, indicating some common activity patterns.

2.3.2. Active Movement

From 60 ms to even one second preceding a voluntary movement, a negative potential in the contralateral sensorimotor area in the frequency of the SMR (8-14 Hz) has been observed and referred as the "pre-movement ERD" [Pfurtscheller & Neuper, 2006]. Several studies demonstrated that after movement onset, synchronization (ERS) in the ipsilateral- as well as in surrounding, not required, contralateral areas could be seen, whereas in the corresponding contralateral region the desynchronization continues until the end of the motor sequence (ERD) [Alegre et al., 2004]. This activation pattern has been associated with the concept of interhemispheric balance or focal

ERD/surrounding ERS concept, according to which the less involved ipsilateral motor area neurons as well as the surrounding contralateral regions are deactivated in order to increase the gain on the required active regions [Müller-Putz et al., 2007; Cassim et al., 2001; Hummel et al., 2002; Pfurtscheller & Neuper, 2006] (see table 1 for an activation overview). This hypothesis could also explain the more bilateral activation pattern in stroke patients during attempted movements, as they need to compensate the lesioned ipsilesional brain parts with activation from surrounding and corresponding contralesional brain parts [Johansen-Berg et al., 2002]. After movement offset there is again a positive potential which may reflect the inhibition of the motor cortex after termination of the intended movement as well as reafferent sensory projections to other motor-related areas acting as proprioceptive feedback [Lee et al., 1986; Müller et al., 2003; Müller-Putz et al., 2007].

2.3.3. Passive Movement

In a passive movement, voluntary planning and preparation processes are missing and the afferent somatosensory components (skin mechanoreceptors, muscle spindles and joint receptors) produce SMR variations alone being these similar to the observed during active movements [Alegre et al., 2002; Keinrath et al., 2006].

In a PET study Mima and his colleagues (1999) compared active and passive movements observing activity in the contralateral primary and secondary somatosensory cortex active during passive movements, while the classical motor network including the primary motor cortex, the supplementary motor area, the premotor cortex, the cerebellum and the basal ganglia were active during volitional movements. They concluded that during passive movements there is a lack of somatosensory attention, necessary and present during active movements for movement control. Several groups observed similar activation relations, using EEG and ECoG data, between executed and passively performed movements [Lee et al., 1986; Müller-Putz et al., 2007]. A predominant desynchronization was presnt already some milliseconds before active movement onset reflecting a planning and preparation process, whereas before passive movements (elicited by a robot or functional electrical stimulation (FES)) this desynchronization was absent. We found recently similar results in a study analyzing the neural correlates during passive and active movement, motor imagery, FES evoking movement and FES without evoking movement [Cho et al. 2011].

2.3.4. Motor Imagery

Motor imagery is defined as mental simulation and rehearsal of movement without a joint overt action [Grezes & Decety, 2001]. The cognitive process of motor imagery does engage some supraspinal structures, but must not result in any spinal motor neuron activation [Stinear et al., 2006]. But even this definition does not satisfactorily differentiate among the various forms of movement imagination, as the neural response clearly differs depending on the perspective of the imagination and the used strategy. It has been proved that kinaesthetic motor imagery, described as a "first person process" involving the feeling that task performance produces in oneself, elicits very similar brain activity patterns to the obtained during active movement execution [Neuper et al., 2005].

Neurophysiologically, the neural system used for the execution of a movement has been proved to be equivalent to the activated during the kinaesthetic imagination of these same movements [Lotze et al., 1999], although the activation was stronger during active movements [Jeannerod & Frak, 1999; Grezes & Decety, 2001; Pfurtscheller & Neuper, 1997].

The observation of movements was found to have an impact on the activity in sensorimotor areas, reflecting processes of motor preparation and motor programming and activating the premotor cortex, the supplementary motor area (SMA) and the frontal cortex [Grezes et al., 1998].

When addressing the relevant activation components in relation to active and passive movements, motor imagery follows very much the same neurophysiological patterns as active movements, except from the overt execution of the movement. It is still unclear whether the primary motor cortex (M1), predominantly responsible for the final motor execution, is also engaged during the imagination of a movement or not. Most studies postulate the S1, the SMA, the cerebellum, the premotor- and the prefrontal cortex to be active during motor imagery [Sharma et al., 2006]. When it comes to the M1 area, some studies suggest an apparent but weaker involvement of M1 [Grezes & Decety, 2001; Jackson et al., 2003; Kasess et al., 2008; Lacourse et al., 2005], while others negate its engagement with the argument that motor imagery is primarily related to the planning phase of a movement rather than to the final execution [De Vries & Mulder, 2007; Dechent et al., 2004]. Hence, it might be the case that the primary motor cortex is not necessary for an accurate movement representation in the brain, but it might be co-activated.

As a review of observed brain ERD/ERS using EEG data, an ERD before the beginning of an active or imagined movement is present. During passive, imagery or active movements ERD is always present in the ipsi- and contra-lateral hemispheres, although right at the beginning of an active movement an ERS occurs. The ERD observed during tasks showed to be stronger in the contralateral hemisphere. Regarding ERS, the beta rebound is present in all submodes, active, passive and motor imagery, after the cessation of movement or imagery (See Table 1).

Table 1. Literature review on neurophysiological activation of active-, passive- and imagined movements prior to- and during their execution in the mu and beta frequency bands. X stands for activation strength.

	Active Movement			**Passive Movement**			**Imagined Movement**		
	Prior	During	Post	Prior	During	Post	Prior	During	Post
ERD									
Contralateral	xx	xxx	-	-	Xx	-	xx	xx	-
Ipsilateral	-	xx	-	-	X	-	-	x	-
ERS									
Contralateral	-	-	xx	-	-	Xx	-	-	x
Ipsilateral	-	-	x	-	-	x	-	x	X

(References: Müller et al., 2003; Pfurtscheller & Neuper, 1997; Alegre et al., 2002, Keinrath et al., 2006)

In my work, I designed and developed an EEG BCI in order to control on-line a robotic hand orthosis, therefore receiving continuous haptic feedback through the mechanoreceptors in the hand joints. In this work I studied how a motor imagery based BCI performance is influenced by the haptic afferent activity and how would different brain modes (not imagery) perform with a classifier defined for motor imagery related activity. Furthermore, I analyzed the neural correlates of the different motor related brain modes-submodes are in the time–frequency domain and compare them in order to find out differences that could make us differentiate between volition and passive action before, during and after a movement cause by the developed haptic-BCI.

2.3.5. Signal Processing

- Online:

The EEG activity used by the BCI platform from the hand (fixed to the orthosis) motor imagery neural correlates were processed at predefined electrodes and frequency bins determined by the R-square values obtained in the screening session. The spatially filtered EEG activity from each electrode was modeled as an autoregressive (AR) process [Nijboer et al., 2008b] over a normalized 500 msec sliding temporal window with an overlap of 120 msec. The power spectral density of the AR-model for each electrode was computed to calculate the mean mu-band power in each chosen frequency bin. The BCI software maintained a history of the selected channels and frequencies (following the r^2 analysis of the screening data) power amplitude estimate from each trial and assigned this to a distribution representing observations for each target (or orthosis action) condition in our case "GO" or "NO GO". If more than one channel or frequency bin was chosen a linear combination of the selected features was used to generate the power amplitude estimate distribution. The classification threshold, defined as the zero mean line at the midpoint of the distance between means of the two distributions (GO and NO GO), was adaptive to account for changes in the shapes of these distributions over the course of training. The BCI2000 classifier output sent an output every 80 msec and 5 consecutive outputs decoding the same class were needed in order to send the orthosis a no-move (zero velocity value) or a move (positive velocity) command.

- Off-line:

<u>Pre-processing:</u>

The EEG data used for the off-line analysis was band pass filtered between 2 and 45 Hz. EOG artefacts were corrected following Gratton & Coles algorithm [Gratton et al., 1983]. Data was epoched for each class from -2.5 sec to +5.5 sec being the "GO" at time 0 sec. Corrupted trials were identified and rejected using 2 different statistical methods using EEGLAB software [Delorme & Makeig, 2004]: 1) joint probability and 2) kurtosis. When using the joint probability method, by determining the probability distribution of values across already epoched data, one can compute the probability of occurrence of each trial. Trials containing artifacts are considered as improbable events and thus may be detected

using a function that measures the probability of occurrence of trials. In my analysis thresholds are expressed in terms of standard deviations (SD) of the mean probability distribution calculated both to single electrodes (local threshold) and the collection of all electrodes (global threshold). Using the Kurtosis method data abnormally distributed was rejected. Kurtosis is also known as the fourth cumulant of the distribution (the skewness, variance and mean being the first three). A high positive kurtosis value indicates an abnormal (high peakedness) distribution of activity in a data epoch, while a high negative kurtosis value indicates abnormally flat activity distribution. Once more, single- and all-channel thresholds are defined in terms of standard deviations from mean kurtosis value (local and global thresholds). Trials exceeding a local threshold of 3 SD and/or a global threshold of 5 SD, were consider as contaminated epochs for both joint probability and kurtosis based rejection methods.

The EMG data was filter using a high pass filter at 10 Hz, bipolarized, rectified and epoched from -0.5 to +5.5 sec being to respect to the "GO" cue for every class (motor imagery, motor imagery with proprioceptive feedback, passive and active movement and rest). A sliding window of 200 msec with an overlap of 20 msec was used to calculate the wavelength of the signal for every class [Tenore et al., 2009]. The class rest was used as reference to define a threshold that being crossed implied EMG activity. The mean and standard deviation of the rest class wavelength was calculated and all trials in which the data exceeded 2 SD from the mean were disregarded and not used to calculate the cleaned resting EMG mean and SD used for the detection of unwanted EMG activity in the other classes. All trials of any class in which the extracted wavelength value exceeded 3 SD from the cleaned class (rejection threshold) were considered to present EMG activity and therefore used to ignore the correspondent EEG data during the off-line analysis. During motor imagery, motor imagery with proprioceptive feedback, passive movement and rest classes all the electrodes on both arms were used for the rejection, since no EMG activity was desired in any arm. On the other hand during the active movement class, the electrodes on the resting arm were used to reject trials with EMG activity and the electrodes on the moving arm were used to control for the presence of the desired movement rejecting trials in which the task was not performed correctly.

The BCI performance:

To analyze how the performance of a motor related BCI could be influenced by the different motor modes-submodes and by the feedback contingency, in addition to the online classification translated into orthosis movements (class 2), we simulated the performance the subjects would have

obtained if the orthosis would have moved during every motor mode in an online setup. For example, how would have been classified the brain activity elicited during passive movement, if the classifier set up for motor imagery would have been used to move the orthosis. Furthermore, several performance measures indicating different phenomena within the SMR modulation were calculated off-line for all the brain modes-submodes to detail our analysis.

1) Percentage of time the orthosis was or would have been moved during a trial (PT). This performance measure reflects the ability of the subject to decrease or maintain the SMR power during a trial.

2) Maximum consecutive time the orthosis was moving per trial (MaxC). This measure represents the longest period of time the subject was able to decrease or maintain continuously SMR desynchronization within a trial.

3) Number of orthosis moving onsets switching from not moving to moving per trial (OnS). This measure reflects how many times the subject needs to overcome an increase in power during a trial to move the orthosis.

4) Latency to the first onset of orthosis movement per trial (OnLat). This measure represents the reaction time of the subject in producing an orthosis movement (SMR desynchronization).

5) Classical performance measure of reaching target, i.e. position of the cursor at the end of the trial, considering a successful trial if the target was reached (ReTa).

These performance measures were calculated simulating an online scenario without EEG or EMG artefact removal and after removal to explore the influence of data contamination. During motor imagery class controlling the orthosis, I expected to observe feedback contingency effects in BCI control producing a learning effect in the contingent feedback groups having a significant higher BCI performance in the contingent positive group. No learning effects were expected in the sham feedback group. These effects were expected to be stronger for PT and MaxC since we assumed that the visual and proprioceptive feedback (time orthosis moving) the subjects received was the easiest way to perceive good correct or incorrect control of the online proprioceptive BCI. The OnS feature might indicate the interference of the proprioception related brain activity bias in the BCI and if no Bias occurs we hypothesized could be a good feature indicating orthosis movement initiations and therefore significant desynchronizations. Changes in OnLat were only expected to be significant comparing the

contingent negative with the other two feedback groups since is based in synchronization and not in desynchronization which is what naturally occurs. Since our online approach is based on a continuous increase or stabilization of a desynchronization this does not necessarily have to be correlated with ReTa and therefore no significant changes were expected besides the difference between contingent negative and the other feedback groups. Nevertheless a better ReTa was expected for the contingent positive since the orthosis movement should increase the desynchronization effect.

During the rest of the motor mode-submodes (motor imagery alone, passive and active movement and rest) no significant changes between groups were expected.

2.3.6. Results

- Statistical analysis

For each of the below defined performance measures (both for the online scenario and for the artefact removal scenario) ANOVA with two repeated measures (class and session) and three groups (in-between factor) was performed to study main effects (session, class, group) and interactions (session x class, group x class, group x session, group x session x class).

Levene's tests for the homogenity of error variances among groups were done for all combinations of class and session. For all performance measures there were none or only few violations of the Levene-tests. Since the number of subjects was less than 10 in each group and the number of performed tests was 20 slight violations were ignored and the error variances were assumed to be homogeneous.

Mauchly's tests for the sphericity were done for the repeated measures factors and in case sphericity was violated significance tests were Greenhouse-Geisser corrected.

In this exploratory study we furthermore performed several planned contrasts to separately identify effects between the sessions, classes and groups.

- To identify learning over the 4 different BCI sessions we performed ANOVA of the sessions among each group for each class separately. Mauchly's tests for the sphericity were done for the repeated measures factors and in case sphericity was violated significance tests were Greenhouse-Geisser corrected.

- We performed ANOVA of the classes for each of the groups and Bonferroni-corrected pairwise comparisons to identify main effects of the factor “class” and the source of it. The performance measures of the different sessions were combined for this step of the analysis.

- To study the differences between groups the performance measures of the different sessions were combined and for each class separately we performed ANOVA of the groups and Bonferroni-corrected multiple comparisons.

A statistical analysis was peformed to study session effects (learning) for every motor mode-submode. A significant group effect was found for motor imagery alone and motor imagery with feedback tasks for all performance measures before artefact removal (being always $p<0.003$) as expected but was absent when comparing the latency to the first orthosis movement onset (OnLat). This indicates that after the go cue the time needed to move the orthosis was not significantly different between feedback groups and suggests that an initiation based therapy in which the robot moves after the first detected onset would not show any significant difference in performance between feedback groups using our classification approach.

When analyzing every feedback group (contingent Positive (CP), contingent negative (CN) and sham) and movement class the only significant session effect ($F(3,24)=4.406, p<.013$) was an increase in number of onsets (OnS) during motor imagery alone (class 1) for the simulated online performance (no artefact removal used), only present in the contingent positive feedback group. This effect on the motor imagery task (class 1) indicates a significant implicit learning effect just present in the contingent positive feedback group. The subjects were trained and rewarded for motor imagery and therefore learning was expected to be present for Class 2 (motor imagery class with proprioceptive feedback) and maybe class 1 because the same task was performed although the feedback was only present in class 2. Despite of a positive trend in the learning curve during class 2 and Class 4, the high variance in performance on both tasks led to no significant learning effect. This result suggests that movement and therefore proprioception brain activity might impede a significant increase of BCI performance in time or that more sessions are needed to obtain a significant session effect during motor imagery task with proprioceptive feedback. However, as we can see in Fig. 9 and 10 the overall performance was higher for classes 2 and 4 on average, indicating a positive influence of proprioceptive brain activity on BCI performance. Interestingly, although no significant effect was found for the contingent negative group, there was a clear increase ($p=0.06$) of MaxC and PT ($p=0.08$) during the rest condition. Subjects in this group tend to

increase the power of the electrodes and frequency bins used in their classifier synchronization during rest to improve their orthosis control.

The learning effect was analyzed for every healthy volunteer independently comparing the first session performance to each of the other sessions using the Kruskalwallis test (non-parametric) Bonferroni corrected for multiple comparisons. In the contingent positive feedback group 3 participants showed statistical significant increase and 2 showed significant decrease in MaxC and PT during motor imagery task alone (class 1). To be noticed is that the subjects presenting significant decrease or no significant change presented high values of performance. During motor imagery task with proprioceptive feedback (class 2) 2 participants showed significant increase and another 2 showed significant decrease in MaxC only before off-line artefact removal. In the non contingent feedback group nothing was significant for any of the performance measures and any motor mode-submode. Interestingly in the contingent negative group 2 subjects showed significant changes during rest. These results together with the feedback groups learning effect described before, suggest that the participants were able to learn how to increase the control of the orthosis in the contingent positive group while in the contingent negative group they tried to improve performance synchronizing more their SMR during rest.

When comparing group performance measures averaged along sessions we observed that during class 1 (Motor Imagery), the percentage of time the orthosis was moved (PT) (CP-CN: $p<0.0001$; CP-Sham: $p<0.027$) and the number of orthosis movement onsets (OnS) (CP-CN: $p<0.0001$; CP-Sham: $p<0.0001$) were significantly much higher (Bonferroni-corrected post-hoc-test) for the contingent positive compared to the contingent negative and sham feedback groups ($p<0.0001$) (See Fig. 10 and Fig. 11). On the other hand, after artefact removal just OnS showed significant higher values (CP-CN:$p<0.0001$; CP-Sham: $p<0.001$) for the contingent positive compared to the sham and to the contingent negative feedback groups (See Fig. 12). The maximum amount of time the orthosis was moving continuously per trial (MaxC) (CP-CN: $p<0.001$) and the reaching target accuracy (ReTa) (CP-CN: $p<.004$) performance measures were significantly higher for the contingent positive compared to the contingent negative feedback group, and higher but no significant compared to the non contingent feedback group (CP-Sham: $p<0.073$). No significant difference was found when comparing sham and contingent negative feedback groups. This was also the case after artefact removal for PT (CP-CN: $p<0.001$; CP-Sham: $p<0.095$). No significant difference between sham and contingent negative feedback group indicates that synchronization of the SMR for the contingent negative group and desynchronization for the non contingent group resulted in similar BCI performance. Basically the

performance was higher for the contingent positive group during the motor imagery alone task, but only significant for the number of onsets, while the difference in the percentage time moving the orthosis was negatively affected by removing EMG contaminated trials.

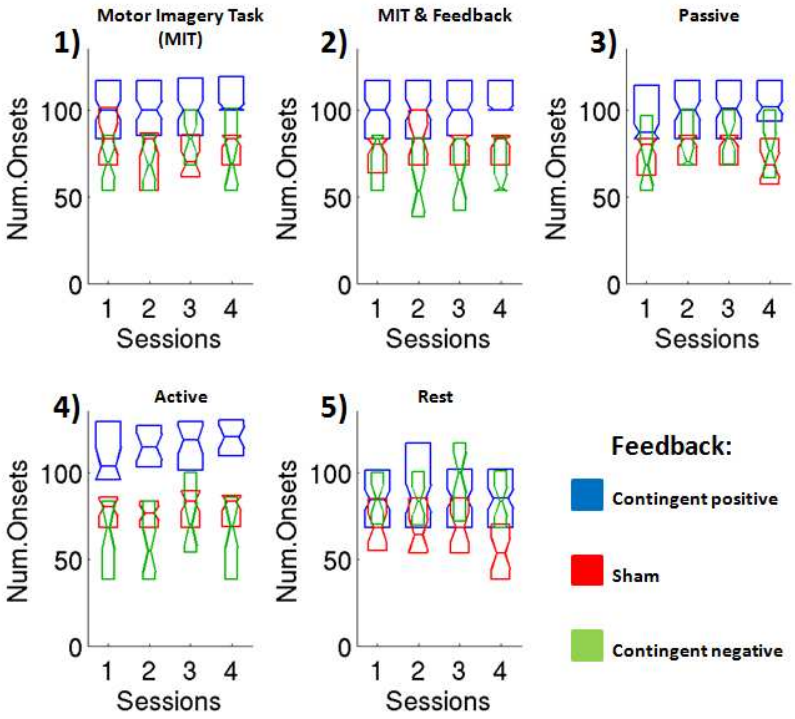

Fig. 10. Number of movement onsets of the orthosis without removing EEG and EMG artefacts (On-line simulation). In blue the contingent positive feedback group, in red the sham feedback group and in green the contingnet negative group. The Y axis represents the number of onset per hundred trials. The X axis represents the number of sessions (separate days of training). Median, first and second quartile of the data are represented by the horizontal lines of the boxes.

During motor imagery with proprioceptive feedback (C2) and during active movement (C4), PT (C2: CP-CN: $p<0.0001$; CN-Sham: $p<0.001$; C4: CP-CN: $p<0.002$; CN-Sham: $p<0.019$), MaxC (C2: CP-CN: $p<0.0001$; CN-Sham: $p<0.0001$; C4: CP-CN: $p<0.006$; CN-Sham: $p<0.025$) and ReTa (C2: CP-CN: $p<0.0001$; CN-Sham: $p<0.0001$; C4: CP-CN: $p<0.012$; CN-Sham: $p<0.034$) performance measures were significantly lower for the contingent negative group compared to the contingent positive and sham groups, although these performance measures did not show significant differences between the sham and contingent positive groups (See Fig. 10 and Fig. 11). After removing artefacts the same effect was found (PT (C2: CP-CN: $p<0.0001$; CN-Sham: $p<0.0001$; C4: CP-CN: $p<0.018$; CN-Sham: $p<0.045$), MaxC (C2: CP-CN: $p<0.0001$; CN-Sham: $p<0.0001$; C4: CP-CN: $p<0.034$; CN-Sham: $p<0.057$), although for ReTa there was no significant

difference. On the other hand, like for the imagery task alone, during imagery task with proprioceptive feedback OnS showed a significant higher value for the contingent positive compared to the contingent negative ($p<0.0001$; artefact removal: CP-CN: $p<0.0001$) and sham (CP-Sham: $p<0.004$; artefact removal: CP-Sham: $p<0.002$) feedback groups for the online simulation and after artefact removal.

There was no significant difference for Class 3 between the groups for any performance measure but the number of onsets (OnS), which in the contingent positive group showed higher values compared to the other 2 feedback groups (CP-CN: $p<0.0001$; CP-Sham: $p<0.014$) before and after artefact removal (See Fig. 12).

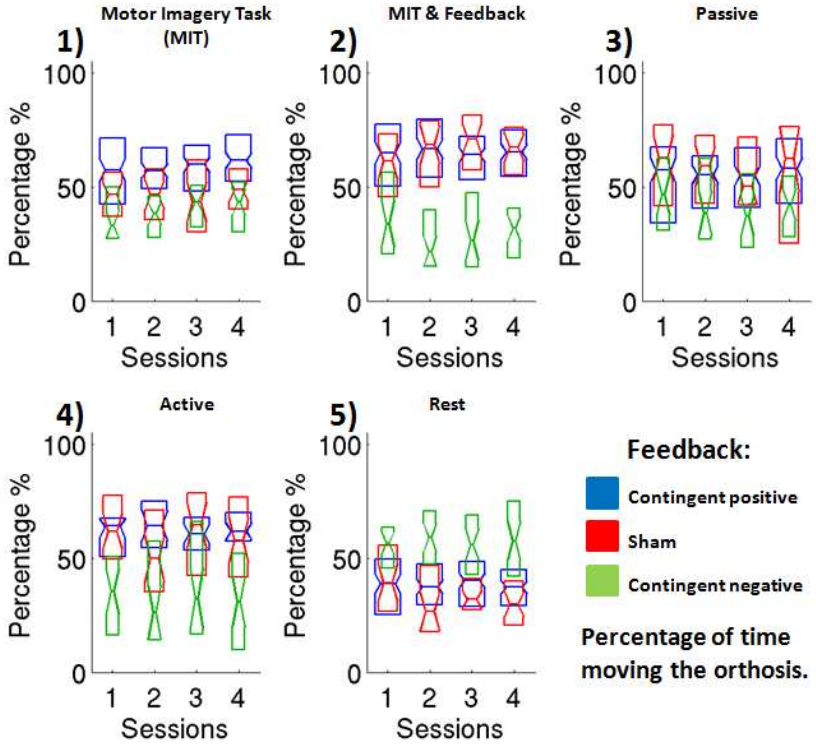

Fig. 11. Percentage of time the orthosis is moving per trail without removing EEG and EMG artefacts (On-line simulation). In blue the contingent positive feedback group, in red the sham feedback group and in green the contingnet negative group. The Y axis represents the number of onset per hundred trials. The X axis represents the number of sessions (separate days of training). Median, first and second quartile of the data are represented by the horizontal lines of the boxes.

We compared the different movement modes-submodes off-line performance for each individual feedback group independently averaging all the sessions together. In the contingent positive feedback group, all the performance measures during class 1 (motor imagery), class 2 (motor imagery

with proprioceptive feedback) and class 4 (active movement) were significantly different (higher for PT, MaxC, OnS and ReTa and lower for OnLat) compared to rest as expected. Although, during motor imagery with proprioceptive feedback (class 2), ReTa and OnLat were not significantly different after EMG artefact rejection, which suggests that without small muscle contractions and with proprioceptive brain activity the average power during the trial (ReTa) and the latency to the first orthosis movement onset increased. During class 3 (passive movement) OnS was significantly higher compared to rest before artefact removal and OnS, MaxC and PT were significantly higher after artefact removal, which means that only passive movement and its afferent generated brain activity would be sufficient to drive our BCI resulting in significant performance results when compared to rest. Furthermore, significant higher OnS values were found for active movement when compared to passive movement before artefact rejection and to motor imagery task with proprioceptive feedback after artefact removal.

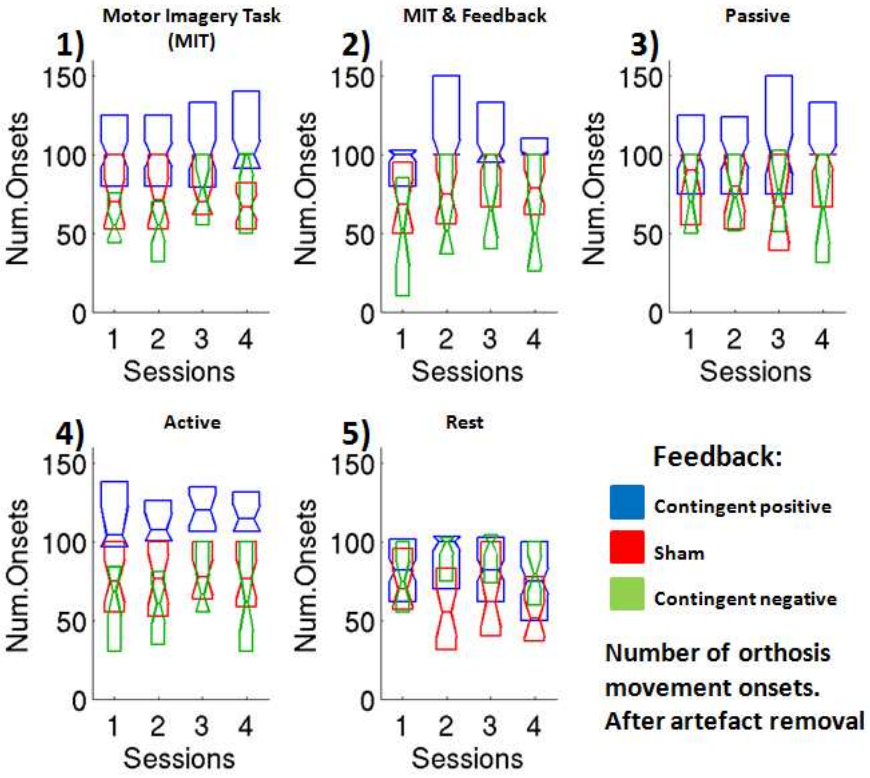

Fig. 12. Number of movement onsets of the orthosis after removing EEG and EMG artefacts (On-line simulation). In blue the contingent positive feedback group, in red the sham feedback group and in green the contingnet negative group. The Y axis represents the number of onset per hundred trials. The X axis represents the number of sessions (separate days of training). Median, first and second quartile of the data are represented by the horizontal lines of the boxes.

When analyzing the contingent negative group we could not find any significant difference between movement mode-submodes using any performance measure if data were not cleaned of artefacts. However after off-line artefact rejection OnLat was significantly shorter in the passive movement when compared with the motor imagery task ($p<0.031$) and the MaxC was significantly lower for class 2 (motor imagery with proprioceptive feedback) when compared to class 3 (passive movement) ($p<0.019$). During class 2 (motor imagery with proprioceptive feedback) subjects showed significantly lower ReTa ($p<0.030$), MaxC ($p<0.043$) and PT ($p<0.033$) values compared to the resting class. Since in the contingent negative feedback group SMR synchronization was moving the orthosis, these results were expected as they are the opposite of the contingent positive group.

The sham feedback group showed significant higher values of MaxC ($p<0.044$) and PT ($p<0.040$) during class 2 (motor imagery with proprioceptive feedback) when compared with class 1 (motor imagery alone) and significant lower latency (OnLat) when compared to the class 1 ($p<0.044$) and rest ($p<0.049$). This result indicates a clear influence of the proprioceptive brain activity probably due to involuntary muscle contraction during the orthosis movement since no significant differences were found when data was not cleaned of artefacts.

To identify differences between the performance measures of the online scenario and the artefact removal scenario we performed ANOVA of each performance measure for the two scenarios among each group for each class separately. Note that the difference between the scenarios was not taken into consideration as an additional factor in the main ANOVA. When we compared the results of the simulated online performance with the off-line artefact corrected performance (averaging all sessions) we mainly observed significant differences only in the contingent positive group. The ReTa performance measure showed a significant decrease in all brain mode-submodes except for rest, indicating that involuntary EMG activity on both arms helped control the average SMR rhythm desynchronization in each trial. The second performance measure more affected by the artefact removal was the percentage of time the orthosis was moved during a trial, presenting a significant increase during motor imagery alone and passive movement, while during motor imagery with proprioceptive feedback a significant decrease was observed. The maximum consecutive time the orthosis was moved during a trial showed a decrease during motor imagery with proprioceptive feedback and an increase during passive movements. These results together with the percentage of time findings indicate that when no involuntary EMG activity was present it was easier for the users to increase and maintain SMR desynchronization (class 1 and class 3) continuously, suggesting that the involuntary muscle activity on

the contralateral arm could have caused mu band ERS on the electrodes used for feedback [Alegre et al., 2004]. While during motor imagery class with proprioceptive feedback, when involuntary EMG (probably compensating movement initiation and stopping) was not present, the desynchronization could not be maintained. This could be explained by having an ERS produced by movement inhibition of the hand attached to the orthosis [Hummel et al., 2002], which would not be of importance of paralyzed patients and therefore this effect should not be present. The ERS produced could have made the number of onsets increase significantly only during motor imagery with feedback and passive movement after removing artefacts. Since we want to apply this new developed online proprioceptive BCI in chronic paralized stroke patients with little or no arm residual movement any EMG activity reinforcing SMR modulation in the paretic arm would be positive in for BCI control and functional recovery. In the contingent negative feedback group, opposed to the contingent positive as expected, we found significant increase in ReTa performance during motor imagery alone, although a significant decrease during motor imagery with proprioceptive feedback and passive movement was observed. This suggests that either head muscle recruitment or short involuntary muscle contractions on the contralateral arm were used to synchronize the SMR [Alegre et al., 2004]. During rest we found a significant increase of the latency to the first orthosis movement and a significant decrease in MaxC and PT after artefact removal mainly due to EEG related artefacts removal. This indicates the users tried to increase the synchronization probably contracting head muscles.

2.3.7. Discussion and Conclusion

There was a significant group effect when comparing all performance measures but OnLat during motor imagery task alone or with proprioceptive feedback between groups which indicates the importance of the feedback contingency. The non significant group effect when comparing OnLat indicates that in a single onset based therapy, in which the first onset would initiate a passive movement, the BCI performance result would be independent on the feedback contingency. Therefore this performance measure would not be adequate for a motor rehabilitation therapy using our BCI system.

The contingent positive group was the only group showing a significant learning effect performing motor imagery which reinforces the importance of the feedback contingency while using a proprioceptive BCI for enhancing SMR control. However when the proprioceptive feedback was provided

the learning effect was not significant due to a higher variance in performance probably caused by the afferent related brain activity. A higher number of sessions might have resulted in learning effect during proprioceptive feedback. Nevertheless the haptic feedback enhanced performance in general approximating it to active movement levels, which was the aim of our proprioceptive BCI (closing the loop in chronic paralyzed patients in the most natural way).

In the contingent negative group we observed a session effect during rest, indicating an attempt to improve orthosis control increasing the synchronization during rest. However this did not help to improve BCI control. More sessions might have been needed for the subjects to understand the feedback contingency and improve their BCI control consequently.

For all the voluntary motor modes-submodes the performance was significantly higher for the contingent positive group in terms of orthosis movement onsets before and after artefact removal. During passive movement and after artefact removal, significant higher values were found for the contingent positive group. This significant finding together with the active movement results suggest that feedback contingency (proprioceptive paired stimulation) influences the neural motor network enhancing significantly SMR modulation during any motor related mode-submode. These findings would support the use of proprioceptive BCIs to induce neural changes that could be exploited by passive physiotherapy of the same movement, while passive movement alone or non contingent feedback would not produce these neural excitation effects. Furthermore, the performance for all brain mode-submodes but rest was very similar within every feedback group, being just the number of onsets (OnS) significantly higher for motor imagery class with proprioceptive feedback compared to passive movement in the contingent positive group. This indicates than even when enhancing the SMR modulation during passive mode due to the feedback contingency, the performance during the use of the online proprioceptive BCI and therefore the SMR network recruitment and control was significantly higher than during just passive movement. This effect would suggest the use of the here presented online proprioceptive BCI as a tool to enhance excitation and control of the SMR neural network.

Another important difference supporting this result is the significant difference in performance between the rest class and the other brain mode-submodes, only happening in the contingent positive feedback group. The contingent negative group showed only significant PT, MaxC and ReTa higher values during rest compared to the motor imagery task with feedback group, which indicates an interesting implicit learning effect increasing synchronization of the SMR during rest.

We observed some changes in significance for the different performance measures depending on the artefact removal. Although the learning results were not affected by the artefact removal, the group comparison for each movement class and the inter-class comparison within group were slightly affected. We considered that the proprioceptive feedback can be interpreted by the user as number of times they can make the orthosis switch from not moving to moving (OnS), how fast they can start moving the orthosis (OnLat), percentage of time the orthosis is moving during the trial and therefore movement absolute distance (PT) or maximum consecutive time they can move the orthosis (MaxC). From our results when removing artefacts we demonstrated that PT, OnS, MaxC and OnLat while using the developed online proprioceptive BCI in chronic stroke patients would profit of small muscle contraction in the paretic arm if present reinforcing BCI control and excitation of the SMR and would not have to inhibit movements producing short ERS that could negatively influence the BCI control. Furthermore, if clear instructions are presented to the patient and the experimenter trains him in the first sessions not to compensate with contralateral EMG activity we assumed the feedback could be presented online without the need of implementing EMG online artefact removal, although some feedback related to EMG in the contralateral arm might help train the user to avoid unwanted muscle activity.

All in all, we proved that the online proprioceptive BCI system we developed can be used as a biofeedback tool, elicits changes in SMR eliciting learning effects, produces an excitation of the SMR related networks explicitly and implicitly generalizing these effects to any motor related mode-submode, improves BCI control and therefore could be used as an interesting motor rehabilitation tool. Furthermore, we demonstrated non-invasive SMR based BCI applications sensitivity to haptic feedback and in particular how proprioceptive related brain activity enhances our online proprioceptive SMR-BCI performance adding to the SMR excitation through volitional control the proprioception related brain activity. This effect resembles SMR related networks excitation during active movement in a very natural way and therefore makes our approach valid to be used as motor restoration device.

All these observations suggested that a more detailed analysis of the time-frequency domain is necessary to understand how the changes in performance are related to the classifier features (electrodes and frequency bins) and more sophisticated classification techniques need to be tested to see how BCI performance could be affected and generalize for the different brain motor mode-submodes.

The integrated BCI platform presented demonstrates how a high-level cortical control signal can be coupled with a robotic hand orthosis online to enable a user to move his body just thinking about it. The development of effective and natural (using almost the same afferent information as in a normal situation) closed-loop control systems tailored to the low-bandwidth nature of BCI signals could provide a more effective and intuitive tool for motor rehabilitation and for the control of prosthetic devices.

2.4. Neural correlates (EEG) of the different motor tasks and differences between feedback groups in the time frequency domain

In order to understand better why the performances differ between classes and feedback groups we performed a time frequency analysis of the EEG data. I was interested to see how changes in frequency in the different channels and in time could affect the performance of our online proprioceptive BCI. Specially, frequencies in the high theta, mu and beta frequency ranges were relevant to analyze the behaviour of the designed BCI. Therefore I looked for changes in power over time and through frequencies between 3 and 45 Hz. We hypothesized that the brain activity during the control of the proprioceptive BCI would resemble the neural activation generated during active movement. Furthermore, I expected to find significant differences between the brain modes in frequency and time that could be used to design filters to differentiate voluntary intention to move or movement, from proprioceptive brain activation. This could lead to a substantial improvement in the control and assessment of different rehabilitations therapies using motor imagery, passive movements (robotics) and proprioceptive BCIs. With this purpose, after rejecting EOG and EMG artefacts related to compensations from the non therapy involved arm and involuntary movements or "quasi-movements" from the hand attached to the orthosis, several statistical analysis were performed comparing time frequency distributions of the data for different classes and different feedback groups.

2.4.1. EEG Time Frequency Analysis

We performed a time-frequency analysis using a 1.142 seconds sliding window with an overlap of 26 msec. We performed this analysis from 2 sec before to 5 sec after the "GO" cue. The event related

spectrum perturbation was then calculated using Morlet transforms [Daubechies, 1996] using 3 cycles at lowest frequencies and 23.04 at highest, having the 200 msec time period from -1.5 to -1.3 sec before the go cue as baseline for the event related spectra perturbation analysis.

In order to assess significance of within-subject and within-classes we used non-parametric statistics not assuming a known activity distribution. A null hypothesis distribution, used to determine significance thresholds, was estimated accumulating surrogate data (200 bootstrap replications), shuffling the single trial spectral estimates using a two-tailed bootstrap significance probability level implemented in the EEGlab bootstrap method [Burgess & Gruzelier, 1999; Efron & Tibshirani, 1994]. Both sides of the surrogate distribution were used to consider for significance.

Several statistical analyses were applied to the time-frequency data in order to control for significant changes. We calculated the area under the receiver operating characteristic curve (AUROC) [Agarwal, 2005; Hanley & McNeil, 1982] using the 200 msec time period from -1.5 to -1.3 sec before the go cue as baseline for time frequency comparisons. The statistical analysis was done, following Agarwal et al. (2005). Simple R square anaylsis was performed using the BCI2000 off-line analysis toolbox explained in the previous chapter.

2.4.2. Results

We observed typical time frequency desyncronization and synchronization over the expected areas (See Fig. 13). Nevertheless for a more specific anylsis of the significance of the frequency oscillations differences I decided to focus more on the statistical significant changes in time and frequency for the different brain mode-submodes to interpret better BCI performance results, possible bias and future designs.

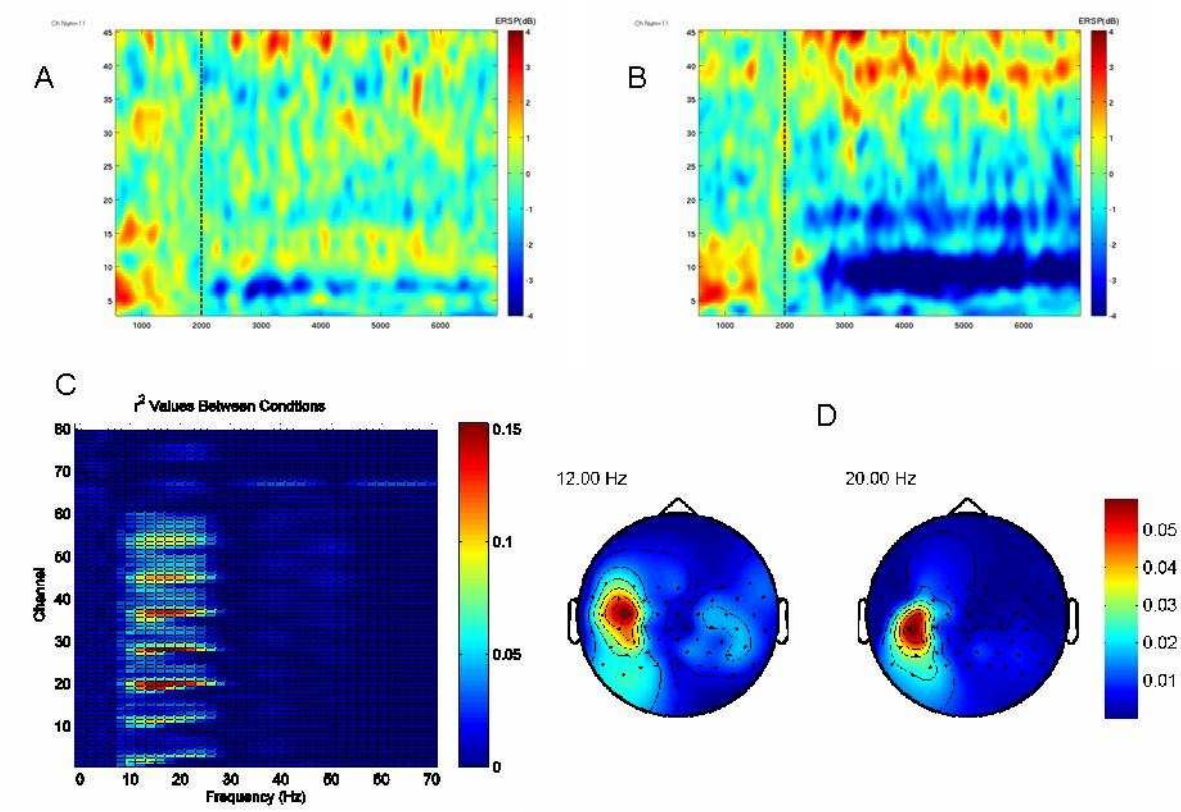

Fig. 13. Neural correlates of two different motor mode-submodes for a representative subject. A) This is the time frequency plot of class 1 (Motor imagery task) from channel FCC3P. The X axis represents times in miliseconds from 0.5 to 7 seconds, being the vertical dashed line at second 2 the time point where the "Go" cue was presented to the subjects. Y axis represents frequencies from 2.5 to 45 Hz. The colours represent the event related spectral power in dB ranging from -4 to 4. B) Time frequency plot of the same channel, for class 2 (Motor imagery task with fake feedback). C) Rsquare plot comparing the 5 seconds of all the trials for class1 versus all from class2. Y axis stands for channels and X axis for frequencies. The color bar indicates the R square values and therefore the statistical difference between the classes. D) Topplots at 12 and 20 Hz of the R square values of class1 versus class2 (all trials averaged). Here we can see the difference of the two components (mu and beta) when averaging the power of the 5 seconds trials at 12 and 20 Hz. The black dots represnts the locations of the electrodes used during the experiments having 60 electrodes placed over the motor

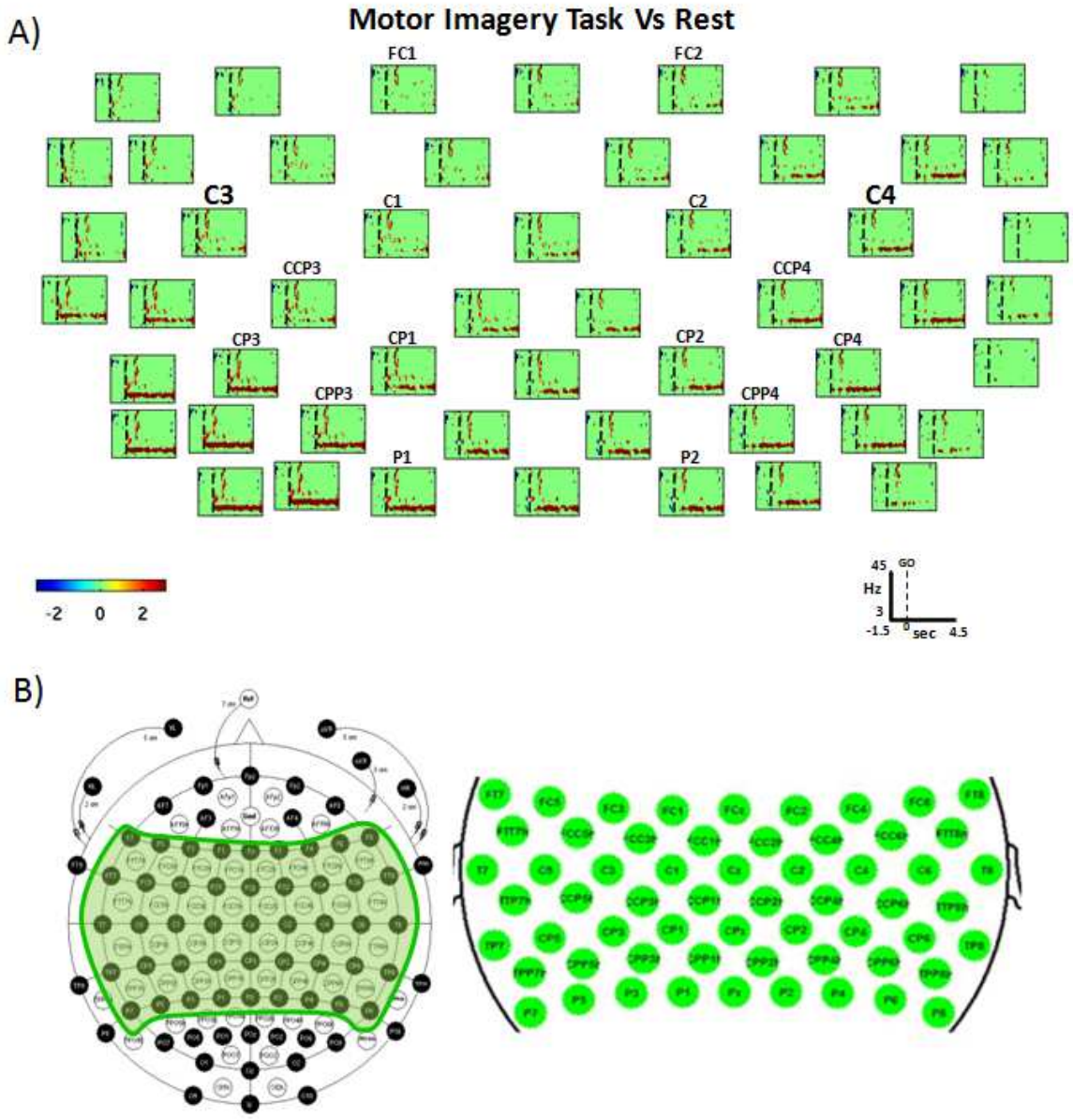

Fig. 14. Bootstrap analysis comparing motor imagery task alone versus resting for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Red and blue color implies desynchronization and synchronization with respect to rest respectively. In Fig. 14.A Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indiates the presentation of "GO" cue at time point 0. The scale for every channel time-frequency plot is presented in the right hand bottom corner, having the X axis representing time (from -1.5 to 4.5 sec) and Y representing frequency (from 3 to 45 Hz). As we can observe the main significant difference in activity is localized in contralateral parietal and ipsilateral frontal areas in the mu band (8-12Hz). Fig. 14.B depicts the location of the electrodes used during the experiment and their location on the scalp following the 10-20 system in a 128 electrodes cap. Those locations were used to place the time-frequency plots of Fig. 14.A

- Motor Imagery alone Vs Rest:

Before the Go cue there were some changes. A significant burst of activity of around 600 msec in the frequency range from 30 to 45 Hz was observed starting 1.5 sec before the beginning of the trial. In the mu (7-11 Hz) and beta (16-18 Hz) bands a short 300 msec burst of significant activity more pronounce in central posterior electrodes was observed right before the "GO". In the theta range (4-6 Hz) a burst of significant activity was observed for the last 200 msec before the "GO" cue, only present in the contralateral hemisphere.

After the Go cue there were many significant differences mainly in the mu band (7-11 Hz) where a clear difference was observed being higher in the contralateral parietal areas and in the ipsilateral pre-motor areas. Only in the parietal contralateral electrodes the significant difference was sustained until the end of the trial. In the ipsilateral hemisphere the significant difference in the mu rhythm was more discontinuous mainly in the first 1000 to 1500 msec after the "GO" cue. In the beta band (16-24 Hz) we observed a clear 450 msec burst of activity only present in the contralateral hemisphere at the beginning of the trial. This significant difference is continuous during the trials as short significant bursts being higher for posterior electrodes in the contralateral hemisphere and for anterior electrodes in the ipsilesional hemisphere. In the high beta low gamma range (20-45 Hz), a clear 350 msec burst of significant different activity was observed 700 msec after the "GO" cue.

- Motor imagery with proprioceptive feedback Vs Rest:

Before the beginning of the trial, a significant 200 msec burst of activity was observed in the high beta range (18-22 Hz) starting 700 msec before the cue and being more pronounced in the contralateral hemisphere. In the low gamma range (30-38 Hz) short bursts (100msec) of significant difference in activity was detected starting 1.5 sec before the trial having a main burst (200 msec) in all electrodes starting 650 msec before the "GO" cue.

During the 200 msec right after the beginning of the trial, a significant difference in activity was observed in the beta range (18-24 Hz) being stronger in the contralateral hemisphere. This significant difference in activity was present during the entire trial, although just by some small significant bursts of

significant difference. A shorter (100 msec) significant burst of difference in activity was found for low gamma range (30-34 Hz) in all electrodes righ after the GO cue was presented and another burst (200 msec) was observed 800 msec after the “GO” cue (30-45Hz). The alpha frequency band (6-12Hz) showed significant differences in all the channels being stronger in parietal areas of the contralateral side and more frontal in the ipsilateral side. The significance effect during motor imagery with proprioceptive feedback condition for mu and beta bands was stronger than the motor imagery alone when compared to rest. Furthermore in the beta frequency band the significant effect was prolonged until the end of the trial. In central contralateral electrodes the significance in the mu and beta band started earlier than in the ipsilateral side, having the significance in beta band an earlier start compared to mu band. While for beta the significance started before the cue and was maintained until the end of the trial, in mu the significance started 300 msec after the “GO” cue in the parietal electrodes delaying the start until 750 msec after the cue in the frontal electrodes. In theta rhythms (4-6 Hz) a short 100 msec burst was observed 800 msec after the “GO” cue in all electrodes and 2.3 sec after the “GO” a short 200 msec burst of significance were observed in all electrodes.

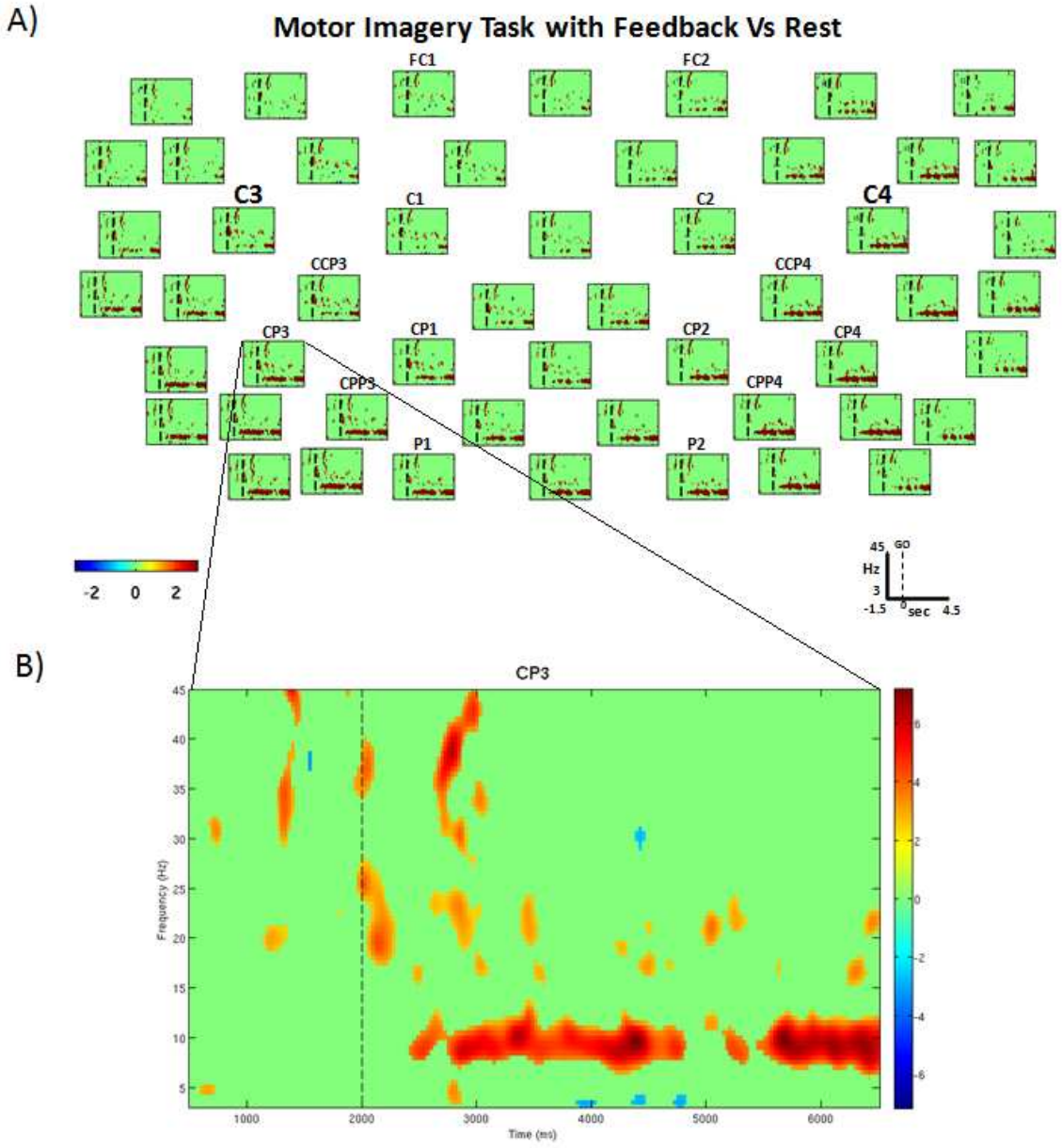

Fig. 15. Bootstrap analysis comparing motor imagery task with feedback versus resting for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Red and blue color implies desynchronization and synchronization with respect to rest respectively. In A) electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indicates the presentation of "GO" cue at time point 0. The scale for every channel time-frequency plot is presented in the right hand bottom corner, having the X axis representing time (from -1.5 to 4.5 sec) and Y representing frequency (from 3 to 45 Hz) B) is an augmented view of electrode CP3 in which we can appreciate better the significant difference in frequency and time between motor imagery with propriocpetive feedback and rest. The color bar represents the signed root mean square (RMS) for this channel, being RMS power the square root of the mean of the square of the power over some the time window used for the time frequency analysis (500 msec).

- Passive movement Vs Rest:

Before the “GO” cue two 250 msec bursts of significant different gamma activity one being 30-45Hz and another 28-30 Hz starting 1 sec and 600 msec before the Go cue respectively were observed in all electrodes. In the beta (18-24) small short bursts (150msec) were observed 600 msec before the “GO cue” only on the contralateral hemisphere. The mu and beta frequency bands presented results in line (but showing higher significance) with the observed for class 1 and class 2, being higher ipsilateral-frontal areas although bihemispheric or even higher in ipsilateral-parietal and starting at the same time in all electrodes as opposed to MIT or MITwF. The mu rhythm significance was wider in the frequency range (6-12 Hz). In the beta band (16-24Hz) significance is stronger compared to MIT but weaker than MITwF. In the low gamma band (30-45Hz) we observed two 200 msec bursts of significance one right after the cue and another 800 msec after it in all electrodes. Two bursts of theta (3.5-7Hz) activity were observed (1.2 to 1.5 and 3.6 to 3.8 sec).

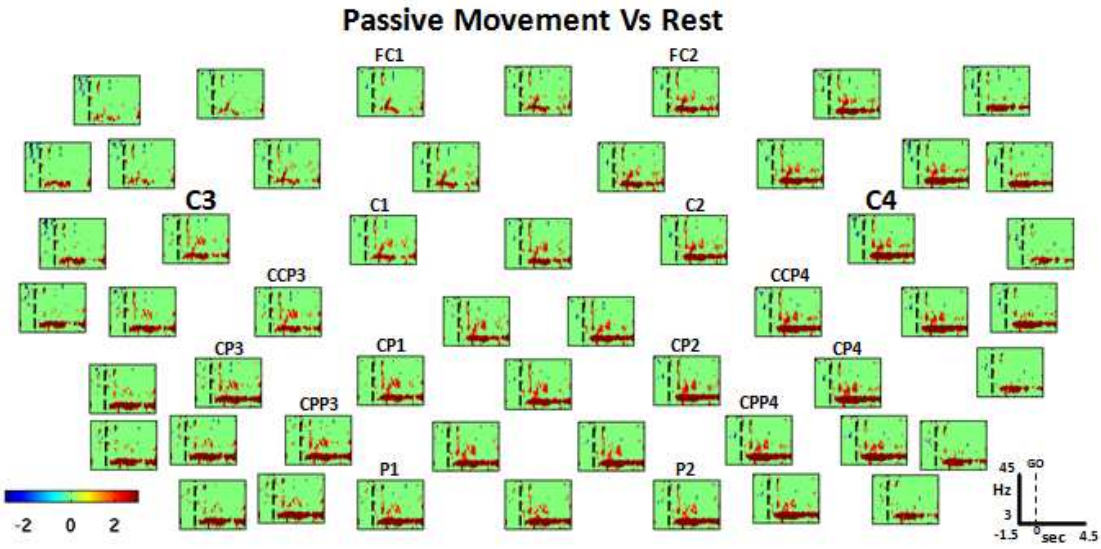

Fig. 16. Bootstrap analysis comparing passive movement versus resting for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Red and blue color implies desynchronization and synchronization with respect to rest respectively. Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indicates the presentation of “GO” cue at time point 0.

- Active movement Vs Rest:

In the last 800 msec before the “GO” cue was presented, we observed a significance difference in the mu (8-10Hz) and theta (4-8Hz) frequency bands in all electrodes, being stronger in more parietal-central regions. Some short (100 msec) bursts of significance difference were observed in the last 600 msec of beta (18-22Hz) activity before the cue more present towards parietal areas, although the bursts were small and not constant in time for all the electrodes. In the low gamma (30-45 Hz) some short bursts (200 msec) were observed before the cue mainly in the contralateral hemisphere temporal electrodes. In the active mode we observed a much narrower significant frequency band in the mu band (8-10Hz) starting 800 msec after the “GO” cue in all electrodes, being the significant difference higher in the ipsilateral electrodes until the end of the trial and absent in frontal contralateral electrodes. We observed that almost no beta activity was significant having some 200 msec in some central-ipsilateral electrodes. A significant burst from 200 to 400 msec was observed in the low gamma band (38-45 Hz) in all electrodes spreading the significant different frequency range of low gamma activity (26-45 Hz) in all electrodes starting earlier in time in parieto-contralateral electrodes and continuing until the end of the trial. In the theta ban (3.5-6Hz) we observed significant differences starting 800 msec after the cue like the mu rhythm being more pronounced in contralateral electrodes. Interestingly the bursts in the theta rhythm during the trial corresponded to bursts broadening the frequency range significance in the low gamma range.

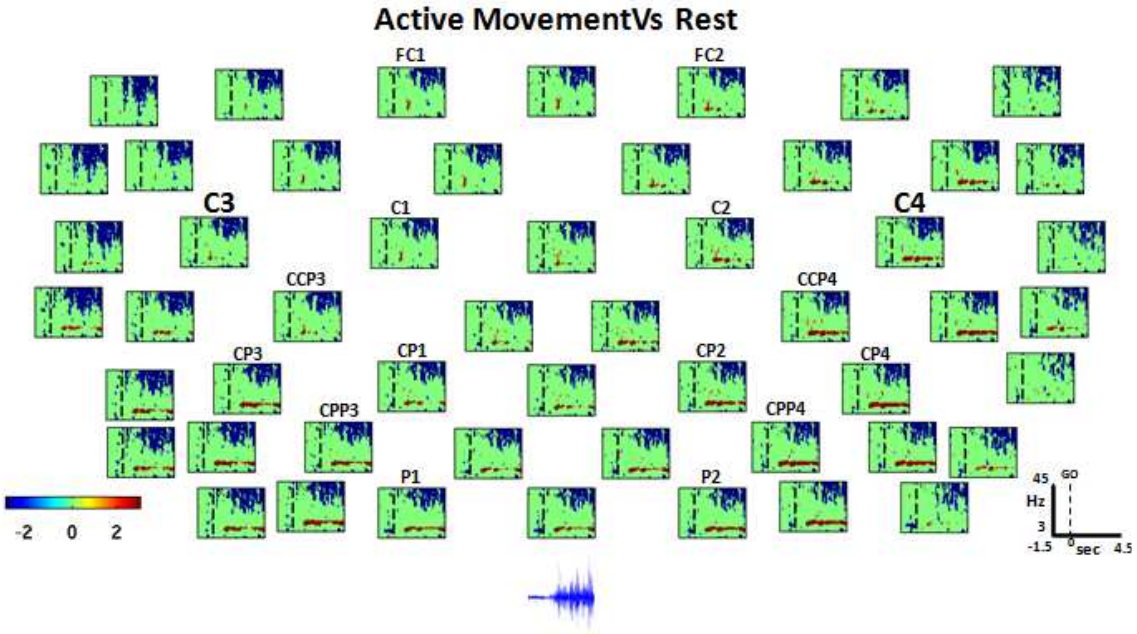

Fig. 17. Bootstrap analysis comparing active movement versus resting for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Red and blue color implies desynchronization and synchronization with respect to rest respectively. Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indicates the presentation of "GO" cue at time point 0. On the bottom of the plot we can see the correspondent raw EMG activity during the active movement movement.

- Motor Imagery Alone Vs Motor Imagery with Proprioceptive Feedback:

Significant activity difference was found in low gamma activity (37-45Hz) in the last 1.5 sec before the "GO" cue present in the contralateral frontal electrodes. A 300 msec burst of significant difference was observed in the mu band (8-10Hz) in centro-parietal electrodes ending 150 msec before the starting of the trial. Right after the "GO" cue a 300 msec burst of significant difference in activity was found in the mu band being present only in the contralateral side for parietal electrodes and on both hemispheres in more frontal electrodes (stronger in contralateral electrodes). Small significant differences were observed in the mu and beta bands during the trial mainly in the ipsilateral electrodes with a clear significant period of 2.5 sec of significant difference in activity in the mu band (8-10Hz) at the end of the trial. This significant difference was observed to be on temporal electrodes in frontal areas

spreading to more central electrodes in parietal electrodes. Some short bursts 100 msec of theta activity (3.5-6Hz) were observed in parietal electrodes starting 2 sec after the “Go” was presented.

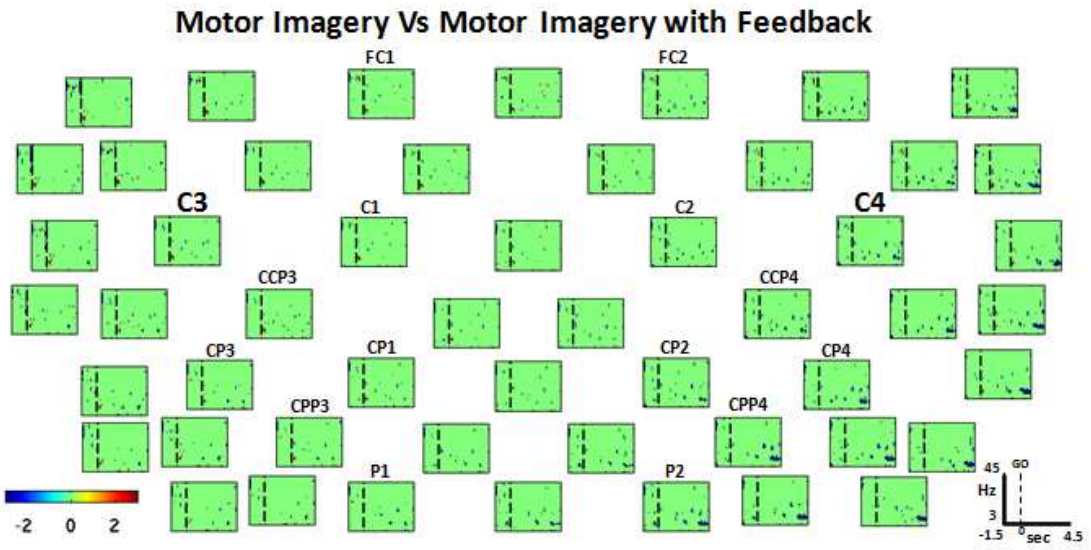

Fig. 18. Bootstrap analysis comparing motor imagery with feedback versus motor imagery for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indiates the presentation of “GO” cue at time point 0.

- Motor Imagery Alone Vs Passive Movement:

In the low gamma frequency range (35-45Hz) a 300 msec burst was found 1.5 sec before the initiation of the trial. In the mu band (8-10Hz) and low beta band (16-20Hz) significant difference in activity was found in the 700 msec previous to the “GO” cue presentation only in centro-temporal electrodes in the parietal area. A theta band burst (3.5-6.5Hz) was observed the last 200 msec before the beginning of the trial. A broad in frequency significance burst (4-12Hz) from 700 to 1500 msec after the trial started being longer in time for mu rhythm and more pronounced in fronto-ipsilateral electrodes. Significance in beta band (18-22Hz) and a narrow mu band (7-9Hz) were presented until the end of the trial in form of small significance bursts mainly in the ipsilateral parietal electrodes. A 400 msec burst of significance was found in the low beta band (14-22Hz) in the 700 msec following the “GO” cue

appearance and only present in the contralateral side. A 250 msec burst of significance was present in low gamma (26-36Hz) 4 sec after the “GO” cue was presented.

- Motor imagery Alone Vs Active Movement:

Just very small mu and beta bursts of significance activity were present in the last 500 msec only before the trial start in the ipsilateral parietal electrodes. Furthermore, during the last 250 msec of that period a burst of theta significance was present in pre-motor contralateral electrodes. During the first second after the presentation of the “GO” cue mu and beta activity were significantly different in parietal area, stronger in contralateral electrodes continuing until the end of the trial only in these electrodes. Significance difference was observed in the low gamma band (38-45) in all electrodes spreading the significant different frequency range very low gamma activity (26-45) in all electrodes starting earlier in time in parieto-contralateral electrodes and continuing until the end of the trial. Some significant brusts of activity were found in theta band (3.5-6.5 Hz) starting 1.5 sec after the “GO” being more pronounced in contralateral parietal electrodes.

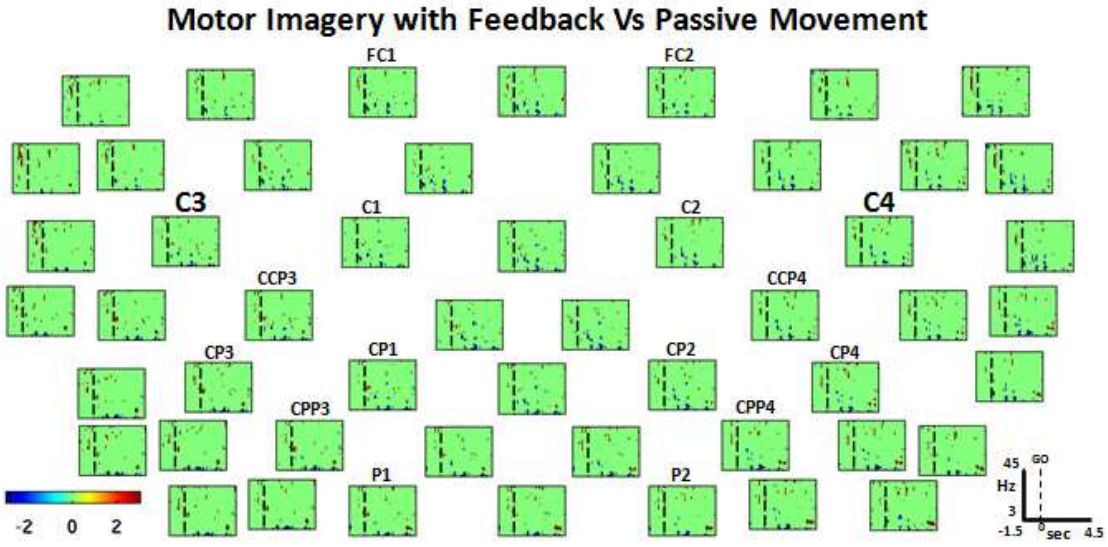

Fig. 19. Bootstrap analysis comparing motor imagery with feedback versus passive movement for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indiates the presentation of “GO” cue at time point 0.

- Motor Imagery with Feedback Vs Passive Movement:

From 700 to 500 msec before the “GO” cue was presented a low gamma-high beta (26-35Hz) burst of significance was observed mainly in frontal electrodes. From -100 to +300 msec a beta (18-22Hz) was observed only in centro-parietal contralateral electrodes. In centro-frontal electrodes on the ispsilesional side we observed some bursts of significant activity in the 10-14Hz frequency band during the first 2.5 sec of the trial. Significant activity was observed in the theta band (3.5-6.5 Hz) starting 1 sec after the “GO” cue and present until the end of the trial being stronger in contralateral parietal electrodes. An 800 msec burst of mu (8-12Hz) activity was observed at after the 4^{th} sec of the trial only present in parietal areas and being stronger in contralateral electrodes.

- Motor Imagery with Feedback Vs Active Movement:

During the last 700 msec before the “GO” cue was presented we observed significant difference activity in mu (7-12Hz) and low beta (14-18Hz) bands being more pronounced central to posterior in the ipsilateral hemisphere for the former and stronger in contralateral in the latter case. From 600 to 400 msec before the “GO” cue a theta (3.5-6.5Hz) burst of significance was present in all electrodes. Immediately after the cue we found a beta (18-24 Hz) burst of significance. During the entire trial we observed burst of significance in the mu (8-10Hz) and low beta (14-18Hz) mainly in parietal contralateral areas starting 400 msec after the “GO” cue. Significance difference was observed in the low gamma band (38-45Hz) in all electrodes spreading the significant different frequency range very low gamma activity (26-45) in all electrodes starting earlier in time in parieto-contralateral electrodes and continuing until the end of the trial. During the last second of the trial there is a clear significance burst of activity mainly in mu theta and some low gamma being higher for parietal ipsilateral electrodes.

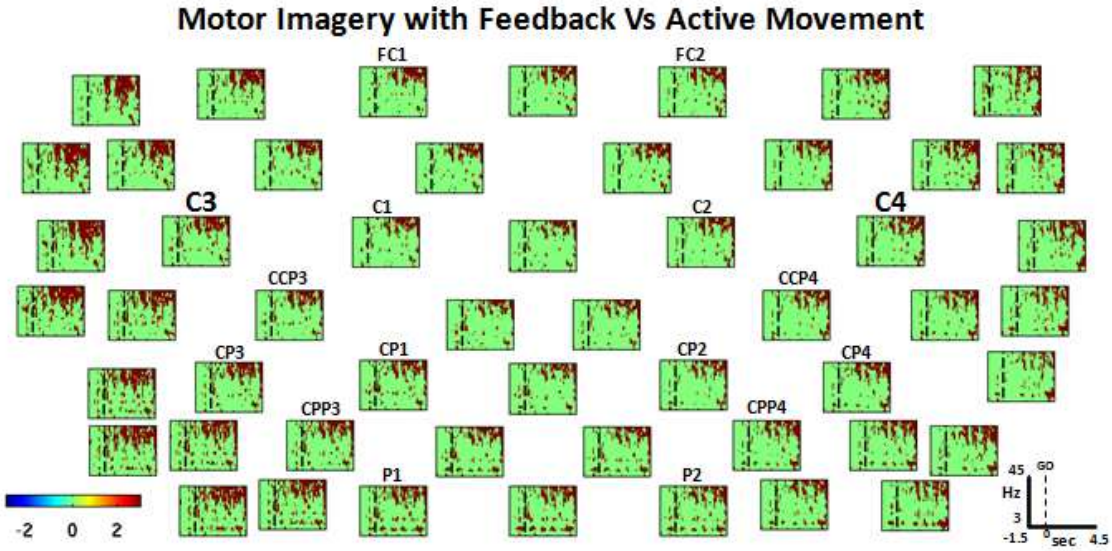

Fig. 20. Bootstrap analysis comparing motor imagery with feedback versus active movement for the contingent positive group subjects only. Everything not coloured green is statistically significant when comparing the 2 classes ($p<0.01$). Electrodes FT7, FC6, T7, C6, TP7, CP6, P7 and P6 are not including in the figure for clarity reasons. The vertical dashed line indiates the presentation of "GO" cue at time point 0.

- Active Vs Passive:

From 600 to 400 msec before the "GO" cue a theta (3.5-6.5Hz) burst of significance was present in all electrodes. For the last 800 msec before the beginning of the trial significant difference in activity in mu and beta bands was observed, being stronger in the mu band and present mainly in parietal regions (as well in frontal ipsilateral areas) with the stronger difference in contralateral electrodes. Significant differences were observed in mu and theta starting 200 msec after the "GO" cue present during the entire trial in form of significant bursts being more significant in ipsilateral areas. In the beta band a 1 sec burst starting immediately after the "GO" cue was present in the central electrodes in the parietal area. Beta activity (18-26Hz) was present in form of short and irreagular bursts of significance during the last 4 sec of the trial mainly in the contralateral hemisphere. A significant burst from 200 to 600 msec was observed in the low gamma band (38-45Hz) in all electrodes being higher in contralateral parietal electrodes. Furthermore, this significant gamma activity was continuous for the last 3 sec of the trial. A clear 500 msec burst of significance was found in the theat band (3.5-7Hz) starting 4 sec after the "GO" cue.

On top of the classical time differences in time between planned or not planned motor modes right before the performance of the task there are clear and statistically significant differences between classes that need to be better analyzed. Since in this thesis I was more interested in understanding the differences during the trial, the first seconds of each condition were averaged to better see overall changes during the feedback period in a topographical manner (See Fig. 21). It is important to notice that the topoplot interpolates between electrodes values, this means that the activity before the first raw of electrodes in pre-motor areas and after the last raw of electrodes in parietal electrodes should be ignored.

As we can see all brain mode-submodes showed very similar topographies in the mu band showing stronger activity in parietal electrodes in the contralateral hemisphere and more medio-frontal in the ipsilateral side. This bilateral difference in activity showed a stronger contralateral activation during MIT, a bilateral during MITwF and more ipsilateral for active and passive movement. Low beta activity (12-18Hz) showed similar patterns as the ones observed in mu during MIT, MITwF and passive movements, although the activation in the ipsilateral side was shifted to more frontal electrodes. This change was stronger for the MITwF mode-submode. Interestingly during MITwF we observed a strong centro-parietal engagement in mu and low beta as opposed to the other three brain motor mode-submodes (MIT, passive and active). During active movement the activity was smaller and more focused in the mu band. Surprisingly during active movement beta activity was not eliciting any clear spatial pattern. In the higher beta band (18-25Hz) MIT elicited only differences in the contralateral hemisphere exactly on top of the motor cortex. The same effect was observed for MITwF, active and passive movement although in these to conditions the difference was expanded to ipsilateral electrodes too.

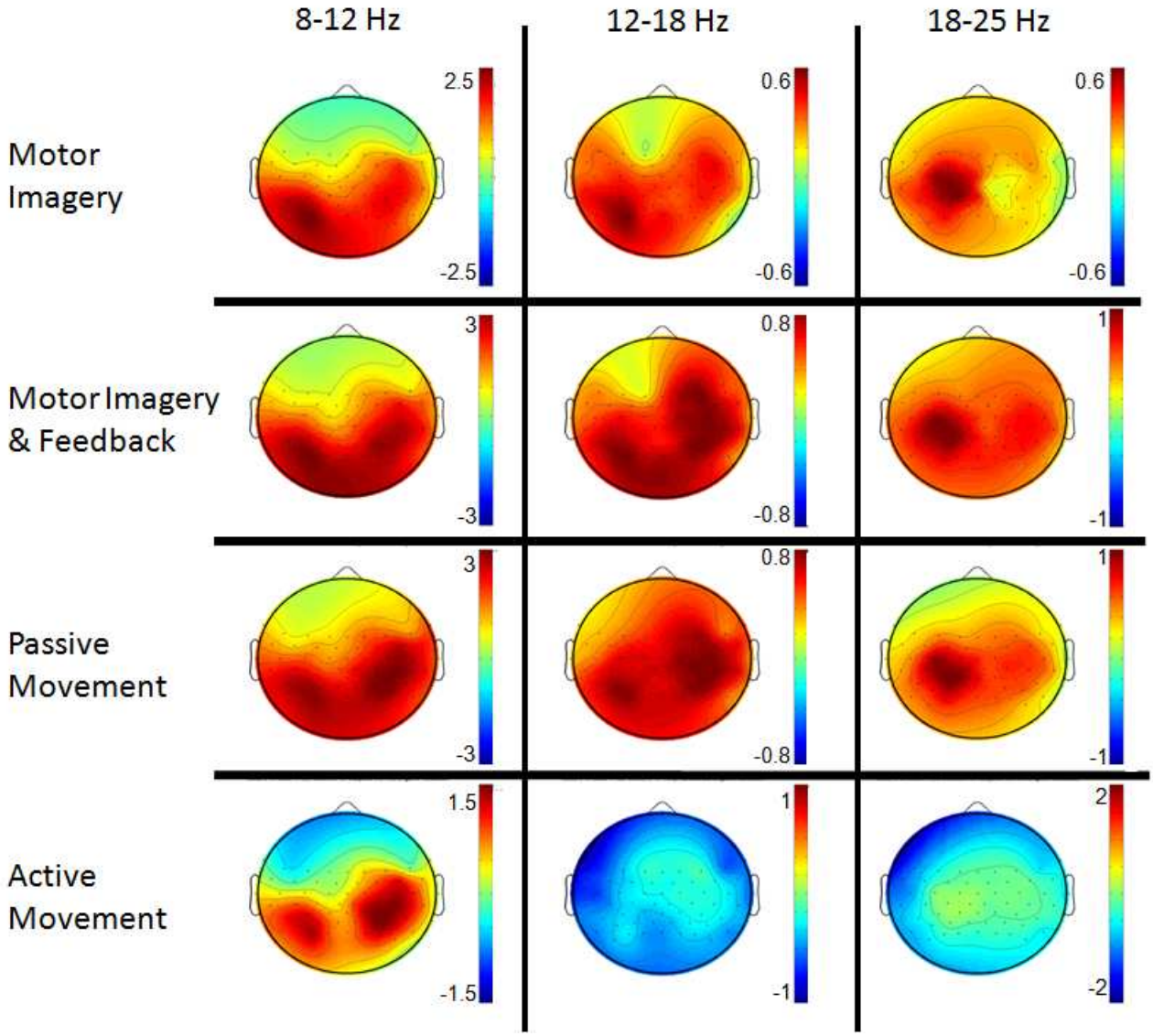

Fig. 21. Topographical representation of the difference in power from every motor mode-submode compared to rest . The power in the 3 different frequency bins (8-12Hz; 12-18Hz; 18-25Hz) was calculated using all the contingent positive group cleaned of artefacts data. To perform the topoplot, the power in the first 4 seconds of the trial were used and averaged using all the trials of all the contingent positive feedback subjects in the 3 different frequency bins. The 60 EEG electrodes placed over pre-motor, motor and post-motor areas are represented with black dots. It is important to notice that the topoplot interpolates between electrodes values (changing the color), this means that the activity before the first raw of electrodes in pre-motor areas and after the last raw of electrodes in parietal electrodes is an extrapolation and should be ignored. As we can see the activity in all classes presents similar spatial distribution varying the values in power (See difference in colorbar scales). Surprisingly, In the passive and active modes a clear and stronger desyncronization happened in the ipsilateral hemisphere. The absence of this activity in the motor imagery alone class suggests proprioception as source of this activation. The absence of low beta difference in activity only happened during active movement electrode.

2.4.3. Discussion and Conclusion

Self-paced limb movements have been mainly described to be accompanied by 3 different types of event-related desynchronization and synchronization (ERD/ERS) patterns on scalp EEG: (i) contralateral dominant alpha and beta ERD prior to movement; (ii) bilateral symmetrical alpha and beta ERD during execution of movement and (iii) contralateral dominant beta rebound (beta ERS) within the first second after movement-offset [Pfurtscheller& Lopes da Silva, 1999]. Imagery of right hand movement can be accompanied by a contralateral beta ERD and an ipsilateral beta ERS [Pfurtscheller & Neuper, 1997]. Voluntary hand movement can result in a hand area ERD and simultaneously in a foot area ERS, and voluntary foot movement can result in an opposite pattern. Such an antagonistic behavior can occur not only between two different modalities but also within the same modality [Pfurtscheller & Neuper, 1994; 1997]. Both patterns are circumscribed and localized close to the hand areas. Common for the enhanced hand area mu rhythm during visual information processing and during foot movement is that in both cases the hand area is not directly involved in the task and therefore the hand area network may be in a deactivated state. The modulation of ipsilateral hemispheric activation during motor imagery, i.e., initial bilateral negativation after stimulus onset and faster decrease of activation than in the contralateral hemisphere, might be due to different accounts: active inhibition of mirror movements or passive interhemispheric cross-talk, e.g., receiving efference copy from the contralateral hemisphere or inhibitory inputs. Regarding the sustained ipsilateral activation during active movements, this might be due to a combination of passive interhemispheric flow, active suppression of mirror movements, and the reafferent sensory input projecting also to the ipsilateral hemisphere via uncrossed fiber tracts [Korvenoja et al., 1995].

In addition to the main investigated motor related frequency bands using EEG (mu and beta), in subdural recordings, contralateral dominant gamma bursts (gamma ERS) have been observed during the execution phase. It is important to notice that induced gamma and beta oscillations are embedded in desynchronized alpha band activity with brisk as well as slow movements [Pfurtscheller et al. 1993, Pfurtscheller and Neuper 1994]. This suggests that a prerequisite for the development of gamma bursts may be the desynchronization of alpha band rhythms. Furthermore, in a recent EEG study, Omlor et al. (2007) found that when comparing conditions of static versus dynamic control of muscular force, the

frequency of corticomuscular coherence shifted from the beta (15 to 30 Hz) to low gamma (30 to 45 Hz) frequency band in individual subjects, indicating that high-frequency oscillations may play a greater role in sensorimotor integration during more dynamic and transient movements.

In terms of spatial distribution, scalp recordings have shown a clear difference between lower (8-10 Hz) and upper (10-12 Hz) mu band frequency components, with a more focused desynchronization pattern of the upper frequency components close to the electrodes overlaying the contralateral hand representation areas [Pfurtscheller & Berghold, 1989; Toro et al., 1994; Pfurtscheller et al., 2000]. In contrast to this, no significant difference between lower and upper alpha band was observed in ECoG [Arroyo et al., 1993; Toro et al., 1994; Crone et al., 1998]. However, both scalp EEG and subdural ECoG recordings have shown a spread of the movement-related alpha (mu) ERD to the parietal lobe [Babiloni et al. 1999; Crone et al. 1998]. Furthermore, Ohara et al. (2000) observed a beta ERD in the 18-22 Hz frequency band on ECoG electrodes in the SMA starting 3.4 ± 0.5 sec prior to a brisk movement, followed by a fast recovery and weak beta ERS. In contrast to Ohara's data, Pfurtscheller et al. (2003b) observed a beta ERD followed by a broadband, large amplitude beta ERS in ECoG recordings from the SMA and a short-lasting gamma ERS after the movement. In addition to the mu parietal ERD, Pfurtscheller et al. (2003b) found also a gamma ERS on subdural electrodes placed over the parietal cortex. Recently, Pfurtscheller et al. (2003c) reported about movement-related beta bursts with frequencies around 26 Hz on midcentrally placed EEG electrodes overlaying the SMA. The finding of a clear difference between the spatial location of the sources generating oscillations in the beta and mu frequency bands suggests a difference in the potential contribution each makes to the preparation and execution of voluntary movement. Different dynamics in the temporal pattern of oscillatory change in these two bands suggest that parallel processes may be occurring in the neuronal network configurations involved in generating these rhythms during movement, with those generating beta rhythms having more of a motor component, while those generating mu rhythms, more of a somatosensory component [Jurkiewicz et al. 2006). In line with these results, Patino et al. (2006) showed that with chronic deafferentation, there is a larger ERD during movement performance, interpreted as effort-related effect since it should be more difficult to perform a movement without sensory feedback. Importantly, this increased negativation is only present in the EEG alpha dynamics, whereas the beta dynamics remained unaffected after chronic deafferentation and in transient ischemia [Schnitzler et al., 1997]. Although in these studies it is not possible to distinguish whether the increased alpha negativation is due to increased effort or due to the removal of the expected sensory input (i.e., larger prediction error requiring increased neural processing,

see below), it is shown that the removal of reafferent feedback does not significantly influence the strength of beta dynamics and at least does not weaken the alpha dynamics.

We observed clear similarities and differences when comparing the different brain motor mode-submodes neural correlates. Significant differences from the class rest were found for all the motor mode-submodes as expected. Clear differences in location, frequency and time were found in all the classes. Since in this thesis we are focusing more our interest in brain computer interfacing for rehabilitation we are mainly interested in significant changes from rest and between conditions in order to classify motor intention as soon, stable and continuously as possible. Therefore we separated the results interpretations in 3 different time frames: a) before and b) immediately after the "GO" cue presentation and c) during the trial. It is well known that feature selection is the most important element within a classification program (Engelhart et al. 1999) and that selecting features automatically can lead to some interpretation errors of the data. Therefore, we wanted to study the neural correlates of the different brain motor mode-submodes to have a prior for feature selection. Since we observed similarities between conditions we separated our analysis in different frequency bands spectral changes that could be used as features to predict and classify the different motor classes and study possible bias in our online proprioceptive BCI. Furthermore, this analysis would help to assess our platform functionality and to propose future improvements. It is important to note that using neurophysiological empirical selected features not only helps to directly link BCI performance to brain activity but to study learning and control of brain rhythms through biofeedback. In order to present our conclusions in a more relevant to the BCI and organized manner I divided my analysis in 3 time windows: 1) preparation period comprising the 1.5 seconds before the "GO" cue presentation starting 0.5 sec after the instructions period in which the subjects were presented with the task to be performed; 2) time immediately after presentation of the "GO" cue comprising the 200 msec after it; 3) Time performing the task during the 5 seconds the trial lasted.

- Preparation period (before the "GO" cue presentation) :

<u>Theta:</u>

During the last 1.5 sec before the presentation of the "GO" cue we observed significant difference in theta spectral activity when comparing rest with motor imagery task (MIT) alone and with feedback (MITF) and active movement. During the last 200 msec before the "GO" significantly different activity was observed only on contralateral electrodes comparing MIT and rest (5-8Hz), while when

comparing MITF the significant different activity (5-7Hz) occurred during 300 msec 1.5 sec before the cue. During active movement theta significant difference (3-5Hz) was observed from 700 to 350 msec before the cue, was relatively constant and stronger mainly in parieto-central electrodes. No significant difference was observed in the theta band before passive movement. Active movement preparation to move elicits significant changes in lower frequencies compared to MIT, MITF and passive movement activation in all electrodes, although the significant difference is from 500 to 300 msec (MIT) and the last 300 msec (MITF and passive) before the "GO cue". These results indicate that in theta rhythms MITF resembles passive movement activity although for the last 150 msec in parietal areas MITF elicited significant changes when compared to passive movements. We suggest that this similarity in activity with the passive movement condition could be due to the expectation of movement of the hand without muscle contraction.

Mu:

Significant differences were found for the last 250 and 800 msec before the "GO" in centro-parietal electrodes for MIT and active movement tasks respectively (MIT: 8-12Hz and Active: 6-10Hz) confirming what was found in the literature [Pfurtscheller & Lopez da Silva, 1999]. The significance in the active condition started earlier and was much stronger that during MIT eliciting significant differences continuously until the "GO" cue presentation. There was significant activation difference when comparing MIT and Active tasks. Interestingly no significant activity was observed for the MITF task resembling more the pre cue activity during the passive movement task in which significant difference was observed as a 200 msec burst 1.5 sec before the "GO" cue. These results suggest that getting ready for the MITF task does not vary significantly the power in the mu rhythm frequency band implying that expecting brain control of proprioceptive activation without muscle contraction does not resemble active movement or motor imagery task pre-"movement" mu band oscillations. In the same line with what we observed in the theta rhythm we suggest that somehow getting ready to undergo movements of the hand without muscle contractions could inhibit preparatory activity in the mu and theta frequency ranges or reduces its significant difference since motor imagery readiness should produce significant difference in spectral changes in those frequencies.

Beta:

Just short significant activation bursts were found in this frequency band before the beginning of the task. In the motor imagery task we observed for the last 250 msec before the "GO" differences in the

16-18Hz band in the centro-parietal electrodes. During MITF, passive and active movement we found significant very short changes (150msec) during the last 500 msec before the beginning of the task in contralateral (MITF 16-22Hz and Passive: 18-22Hz) and parietal electrodes (active: 15-17Hz and 21-23Hz). These results suggest 2 beta band components during task preparation, in which the 18-23Hz might comprise preparation for proprioceptive activation, while the 15-18Hz could correspond to attention to a task or preparation to move maintaining postural state [Hatsopoulos & Donoghue, 2009]. Nevertheless, when comparing passive and MITF activation 2 significant bursts of difference in activity from -700 to -500 and the last 100 msec extending to 300 msec after the "GO" were found at 24-30 Hz and 18-22Hz respectively. While MIT just showed differences right before the cue in low beta 15-18Hz when compared to passive movement, active and MITF showed significant difference in the latter frequency band and from 18-24Hz reinforcing the previously presented hypothesis of having 2 different beta readiness components one for proprioceptive activation (18-24Hz) and another one for attention to a task or preparation to move or elicit motor imagery maintaining postural state. Again in this frequency range we observed that the preparatory activity during MITF resembles more the passive activity than the active or MIT brain activation.

Gamma:

In all conditions 30 to 45 Hz activity was found as short bursts of significant difference in gamma spectral activity when compared to rest. In MITF and active movement, the activity was significant compared to rest during the last 600 msec and 250 respectively. On the other hand passive movement and MIT showed significant changes compared to rest 1.5 to 0.8 sec before the "GO". Furthermore a 28 to 30 Hz 200 msec burst of significance was observed when comparing passive and rest. Only when passive movement was compared to both motor imagery related tasks we saw a significant burst (24-35Hz) from -700 to -500 msec before the "GO". Furthermore, a 300 msec burst (30-45Hz) 1.5 sec before the beginning of the task when comparing MIT with all the other tasks (active and passive movement, MITF and rest) indicating some gamma activity related exclusively to preparation of MIT was observed. This could indicate changes in gamma oscillations due to preparation for movement imagery without movement since the other conditions showed significant difference in activity.

- First 200 msec after the "GO" presentation:

Theta & Mu:

No significant differences were found when comparing rest with MITF, passive and active movement. Only MIT showed significant changes (4-6Hz and 8-12Hz) in the first 150 milliseconds in medial-contralateral electrodes for theta band changes, while in the other brain motor mode-submodes the significance was interrupted (mu rhythm). The significant changes in the mu band were observed in all electrodes being higher in contralateral electrodes for parietal areas and more ipsilateral in frontal electrodes. For passive movement high mu rhythm (12-14Hz) significance was found in medio-frontal electrodes.

Beta:

All brain mode-submodes showed significant differences in this frequency band when compared to rest. While for the MIT and MITF the significant difference was broadbanded (18-26Hz) contralateral and higher in parietal areas, during active and passive the significance difference in activity was in a narrow band (active: 22 to 24Hz and passive: 24 to 26Hz) mainly ipsi-parietal for active and in all electrodes being higher in contra-parietal electrodes for passive. Interestingly when comparing MITF with passive and active movements we observed significant activity (18-22Hz) in only contralateral frontal electrodes and contralateral respectively.

Gamma:

Only a 100 msec burst of significant activity (35-42) was observed for MIT, MITF and passive movement being absent during active movements.

- During the trial:

Theta:

Interestingly during MIT, MITF and active movement a burst of significance was found in all electrodes from 700 to 1000 msec after the cue, presenting MITF and active movement more significant theta activity (3-6Hz) until the end of the trial (although in the MITF this activity was discontinuous). During active movement the activity was more significant than for MITF and more pronounced in contralateral areas although during MITF the significance was higher compared to MIT. During passive movement 2 bursts (1.2 to 1.5 and 3.6 to 3.8 sec) were found (3-7Hz) coincidentally to the open and

close position (stopping the orthosis for 150 msec and changing velocity sign when maximum open position was reached). In this frequency band MITF resembles better the activity during the active movement compared to MIT and passive.

Mu:

This is the frequency band in which more significant activity was found for all the brain mode-submodes when compared to rest. There are several differences between groups being significant frequency band, spatial distribution, latency and continuity and the main differential factors. During MIT and MITF the significant frequency band was 6 to 10Hz while for active and passive was 6 to12Hz and 8 to 10 Hz respectively, suggesting that low alpha band (6-8Hz) might be directly related with voluntary motor control. The same spatial significant spatial distribution was present in all tasks, being present in all electrodes but more significant in ipsilateral electrodes for frontal electrodes and contralateral for parietal electrodes. This significance could be described as a significance diagonal from contra-parietal to ipsi-frontal electrodes in motor areas (See Fig. 21). Motor imagery task alone was the only brain motor mode-submode showing clear significance from the beginning until the end of the trial, although this was the case only for contralateral parietal electrodes. After the first burst of activity during the first 300 msec of the trial, the significance latency for MIT in the ipsilateral electrodes increases towards frontal areas. This means that the significant oscillations change starts in parietal areas and continues towards more frontal areas being in line with Hatsopoulos and Donoghue (2009) hypothesis of propagating waves, although this was only within the mu band and the case for MIT and MITF and not for active nor for passive. During MIT in medio-frontal electrodes there was a 350 msec significant change in activity being interrupted and reappearing continuously until the end of the trial 1.5 sec after the “GO”. In the MITF the significance starts early in contralateral parietal electrodes (300 msec after the “GO”) and then continues until second 2.1 after the beginning of the trial being this interruption of significance delayed towards central electrodes and even no interruption was observed for ipsilateral-parietal electrodes. In the passive movement mode we observed same latency for the beginning of significant spectral changes (200 msec) in the contralateral hemisphere, while for the ipsilateral side the significance starts earlier in parietal areas propagating towards frontal areas in line with the propagating beta waves in the active condition of Hatsopoulos et al. (2009). This significance was maintained until the end of the trial in medial-ipsilateral electrodes, while in fronto-contralateral electrodes a discontinuity was observed at second 3. The active movement started the latest in showing significance in the mu rhythm starting 800 msec after the “GO” and maintaining it until the end of the trial in parietal areas. This late response in

significance difference when compared to rest could be explained since the reaction time was long for all users as demonstrated in Figure 17. In the active case the continuous significance was only present in the significance diagonal (contra-parietal ipsi-parietal and fronto-ipsilateral), its latency was the same and it was just continuous until the end in the parietal medio-lateral electrodes as opposed what was found by Hatsopoulos et al. (2009). Interestingly when comparing MIT and MITF we found significant differences in mu spectral activity (8-12Hz) for the first 500 msec mainly in contralateral frontal electrodes and for the last 2.5 seconds of the trial in temporo-medial and centro-parietal in the ipsilateral areas. Comparing passive movement and MITF we found in the first 2.5 sec significant differences (10-14Hz) in ipsilateral areas as well as for the last second (8-12Hz) in parietal areas (mainly contralateral). On the other hand, when comparing active movement and MITF we saw regular bursts of significance (8-10Hz) mainly in contralateral-parietal electrodes with a high significance burst during the last 1.5 sec in ipsilateral-parietal electrodes. All this suggests that during the last seconds of the trial there is a parietal activation during MITF with a passive propriocpetive ipsilateral component and a clear volitional motor component in contralateral electrodes. Relevant for motor rhythms based BCI control is the fact that in the contralateral hemisphere, MITF and active movements do not show significant differences when compared to each other, while passive movement shows significant differences during the entire trial from 10 to 12 Hz. This means that classification of mu desyncronization due to active movement or MIT could be differentiated from passive desynchronization when using medio-parietal electrodes on the contralateral hemisphere.

Beta:

Interestingly opposing to most of the previous results commented in the literature almost no significant activity was found during active movement in low beta (16-24Hz) when compared to rest excepting very short bursts of significance mainly in medio-frontal centro-parietal electrodes (SMA) which started after the GO (before movement initiation) and continued during movement in form of short and discontinuous bursts of significance mainly in the first 1.5 sec after muscle contraction started. This goes in line with the results of Ohara et al. (2000) describing beta significant desynchronization prior to an active movement. During MIT and MITF a very significant difference when compared to rest was found for the first 450 msec (MIT: 14-20 Hz and MITF: 20-24 Hz) mainly in contralateral-parietal and ipsilateral-frontal electrodes while during passive movement just the frequency range from 20 to 24 Hz

showed significant changes. This finding indicates that high beta band (20-24Hz) activity during movement onset might be related to proprioception without muscle contraction since on average the onset to the first orthosis movement in the MITF was 250 msec. While for both conditions (compared to rest) significant bursts where found during the trial, we observed high beta significant activity (20-24Hz) only during motor imagery task with feedback similar to what we observed during passive movement. Furthermore, the significant difference in beta oscillations was higher during MITF compared to that from passive movement and MIT suggesting an involvement of volitional motor related neural activity reinforcing beta band significance in the 20 to 24 Hz frequency band. During passive movements 16 to 24 Hz significance was found being broader in frequency and more continuous from 1 to 3.5 sec after the "GO". The beta activity during passive movements was less significant compared to MITF and more significant than MIT. Interestingly when comparing MIT and MITF we found significant spectral changes in the beta band (18-22Hz) mainly in the ipsilateral-parietal electrodes more towards the end of the trial, while if MITF and passive movement were compared we found only significant changes (18-22Hz) in contralateral centro-parietal electrodes during the first 500 msec of the trial. These results suggest that the proprioceptive feedback might help maintain the desynchronization in the beta band when it normally starts decaying in time and that during the beginning of the trial the desynchronization of beta band was significant only during motor imagery but not during active movement. This significance was higher and more continuous during motor imagery than during active movement. Passive movement produced more significant changes in frequency compared to active movement, MIT and MITF suggesting an implication of high beta rhythms (20-24Hz) in proprioception without muscle contraction since this frequency range just showed significant changes during MITF and passive movement. However during MITF the significance was not so broad in frequency and less continuous. In this frequency rangethe MITF condition suggest a combination of passive movements and MIT brain activity.

Gamma:

During MIT, MITF and Passive movement a 200 msec burst of significant desynchronization (30-45Hz) was present in all electrodes 800 msec after the "GO" when compared to rest, while during active movement a short burst of significant synchronization (38-45Hz) from 200 to 400 msec after the "GO" was observed. This significant synchronization continued in contralateral parietal electrodes when mu rhythm desynchronization started to be significant spreading to a broader frequency band (26-45Hz) starting earlier in contralateral-parietal electrodes and sustained until the end of the trial. This latter effect has been already described by Pfurtscheller et al. (2003c) in active movements although it was just

mention as beta activity. The gamma activity in the 26 to 45Hz started together with the mu significant activity only in the contralateral hemisphere being in line with previous research [Pfurtscheller et al. 1993, Pfurtscheller and Neuper 1994]. The significant activity (26-45Hz) started earlier in parietal contralateral electrodes and being delayed towards pre motor electrodes in line with Hatsopoulos et al 2009 theory of propagating waves, while in the ipsilateral hemisphere no delay between parietal and frontal areas was observed.

The spatial activation on both hemispheres, the time, strength and differences between classes and feedback groups suggests the need of proper feature selection to classify the different brain modes and submodes helping to design better motor rehabilitation haptic robots and monitor the user while being in use. My data provides some hints and directions to improve feature selection upon neurophysiological empirical data suggesting the use of contralateral parietal areas mu band activity as the indicated source of features for my particular aim using an online propriocpetive BCI for motor rehabilitation. The presented data demonstrated how passive movement per se elicited significant activity in the mu and beta band to drive our BCI with an acceptable performance. However, this data showed that volitional motor related brain activity together with haptic information (regardless of the feedback contingency) increased the significance of the oscillations change in the mu and beta rhythms being this effect translated into better BCI performance. Nevertheless contingency of the feedback was essential to induce implicit learning and generalize the excitation and modulation effects on mu and beta rhythms during even passive movements. Furthermore when the proprioceptive feedback was contingent (embedded in SMR rhythms) the significant change in SMR modulation increased together with the BCI control.

It is important to notice that significant differences were found before the beginning of the trial and before the movements allowing us to predict activity and therefore speed up classification rate. Furthermore, proprioceptive feedback coming upstream to the brain through afferent pathways due to the hand movements affects positively user control of the BCI system. This afferent information could bias the brain signals used for BCI control. This effect is different than what a passive movement would generate insinuating that it could be directly related to the proprioceptive feedback. This would mean different activation or state of the brain dynamics when having contingent proprioceptive feedback while no active muscle contractions were present. These findings need further study and can raise the question of the existence of a different brain state when activating afferent pathways bypassing brain motor effectors and most of the motor receptors. Significant different brain networks activation only

present during MITF indicates recruitment of different brain oscillations related to volitional control of proprioceptive information.

When using the here presented results in the design of a proprioceptive online BCI for motor restoration in chronic paralyzed stroke patients several aspects should be taken in consideration and further investigated. Motor imagery and motor execution share common networks and generate similar brain oscillations. In the case of paralyzed patients the difference in activation due to motor imagery and intention to move needs to be investigated since the activity while moving actively in healthy volunteers did not elicit broad band activity neither in mu nor in beta bands. The effects of the proprioceptive feedback could help to broaden the significance effect in frequency and therefore help to detect volitional motor brain activity in patients with paralysis due to stroke and help restore motor ability. This could help to improve BCI control during motor execution. Our results show suggest movement or intention to move onset would not suffer from paralysis and therefore initiation control of our BCI should not be problematic.

2.5. Afferent pathways in ALS

To design appropriate BCI interfaces it is necessary to understand the neurophysiological afferent pathways that could be used in order to provide the feedback and therefore enhance learning and performance in the use of the neuroprosthetic device. Therefore, in the case of an ALS patient, we wanted to clarify the physiological and behavioural boundaries between locked-in (LIS) and the completely locked-in state (CLIS) (no voluntary eye movements) through electrophysiological data and to secure brain-computer-interface (BCI) communication. In order to achieve this goal, we performed electromyography from facial muscles, external anal sphincter (EAS), electrooculography and electrocorticographic data during different psychophysiological tests to define electrophysiological differences in an amyotrophic lateral sclerosis (ALS) patient with an intracranially implanted grid of 112 electrodes for nine months while the patient passed from the LIS to the CLIS.

Currently there is a lack of physiological measures to define the transition from the LIS to the CLIS. Furthermore, no standardized scale exists for the late stages of ALS. Once the zero value in the ALS functional rating scale (ALS-FRS) is obtained classification of the disease stage in ALS is complicated and this scale does not differentiate between CLIS and LIS. However, there is a fundamental difference

between the two: communication is still possible within LIS but up to now impossible in the CLIS [Kübler & Birbaumer, 2008; Hinterberger et al., 2005a].

In 1966, Plum and Posner defined the "Locked-in" syndrome as the clinical syndrome due to bilateral lesions of the corticospinal and corticobulbar tracts in the ventral portion of the pons with preservation of the tegmentum, describing a neurological condition of quadriplegia, anarthria and a paralysis of all facial muscles except the vertical eye movements. Consciousness is thought to be fully preserved and can be demonstrated through voluntary blinking. However, LIS is not a homogenous neurological entity but has numerous variations [Bauer et al., 1979]. Kübler and Birbaumer (2008) define LIS as a state of almost complete paralysis with voluntary eye movement control, eye blinks or twitches of the lip. The complete LIS (CLIS) is defined as a condition in which all motor control is lost.

Bauer and coworkers (1979) further differentiate these states: 1) the classical LIS, which refers to total paralysis except for eye movements and blinking, combined with preserved consciousness, 2) incomplete LIS, which refers to a state in which other voluntary motions are present (e.g. movement of thumb) and 3) total LIS, which consists of a total paralysis including paralysis of eye muscles combined with preserved consciousness.

Bauer and coworkers (1979) suggest that voluntary blinking could be a behavioral tool with which a differential diagnosis between the classical LIS and coma and prolonged coma-like states can be made. Furthermore, Bauer suggests that EEG could serve as an electrophysiological tool to differentiate CLIS from coma.

Several other progressive, systemic or traumatic neurological diseases may result in a LIS and CLIS such as ALS, Guillain-Barre, end-stage Parkinson disease, multiple sclerosis, traumatic and toxic brain injury and others with different etiological and neuropathological features. Thus, the enormous variation of LIS and CLIS asks for a physiologically based measure to quantify the degree of the "locked-in" state. ALS seems to be a particularly useful model for this measure because of the frequent change from LIS to CLIS within one patient.

Markand (1976) differentiated LIS from Coma by the presence of EEG reactivity and "alertness" in LIS. However, Kotchoubey et al. (2003) have shown that EEG-reactivity (Event related synchronization ERS, and event related desynchronization, ERD) is sometimes present in Vegetative State (VS).

Eye movement paralysis, sensory dysfunctions and vesicorectal disorders [Yuki et al., 1995] are frequent complications after long respiratory support and paralysis. Therefore, their differentiation power is low as some groups reported patients with ventilation for many years with some patients showing incomplete and variable presence of the above mentioned signs [Hayashi et al., 1991; Okamoto et al., 1993; Yoshida et al., 1992].

The only remaining possibility to retain communication in the CLIS depends on neuroprosthetic devices, particularly brain computer interfaces (BCIs). Successful application of visual or autonomic signals in the LIS was reported only once in a single case using recordings of pH from mouth saliva [Wilhelm et al., 2006]. BCIs depend on differentiable neural signals (i.e. to encode a "yes" and "no" signal). Therefore, a precise characterization and prediction of the CLIS seems mandatory [Kotchoubey et al., 2003]. Peripheral autonomic psychophysiological measures could also be used for communication such us skin conductance responses (SCR), heart rate (HR) and respiration. Patients may signal "yes" or "no" by changing one of those response systems activity. In the paralyzed artificially ventilated ALS patient HR-variability is severely reduced by the paced artificial respiration and lack of muscle activity necessary for HR-increases. Voluntary operant regulation of HR-decrease in ALS seems extremely difficult to learn and uses different psychophysiological mechanisms [Cuthbert et al., 1981] than control of HR-increase. Therefore, HR-control, sniffing or breathing control is not possible in advanced ALS. The situation for SCR in ALS is not clear and no data exist. Skin alterations due to the disease and as a consequence of extended bed rest are frequent [Masur et al., 1995] and may prevent voluntary control. In the patient reported here SCR measured from the palm of the hand was virtually absent, probably correlated with the unresponsiveness of parts of the somatosensory system. Furthermore, late stage ALS and CLIS exhibit sympathetic and parasympathetic signs [Pinelli et al., 1995], decreased heart rate variation [Pisano et al., 1995], alterations of the excretory function of the salivary glands [Giess et al., 2000], and disturbance of the gastrointestinal tract [Toepfer et al., 1997; 1999]. This suggests autonomic abnormalities. Studies using 123IMIBG- SPECT have shown deficient sympathetic cardiac innervations [Druschky et al., 1999] and electrophysiological data demonstrated alterations of the sympathetic skin responses in ALS, indicating a degeneration of sympathetic nerve fibers [Masur et al., 1995].

Postmortem histology of ALS patient's tissue showed neuronal degeneration and loss of Onuf's nucleus in the ventral horns of the spinal cord, explaining alterations in bowel and bladder innervations [Pullen & Martin 1995; Carvalho et al., 1995]. Long-term artificial respiration and feeding compromise and regularize the physiological systems involved.

These findings challenge the previously accepted hypothesis about the non involvement of the striatic pelvic floor sphincter muscles and the survival of the Onuf nucleus motor neurons in CLIS [Carvalho et al., 1995]. However the Carvalho et al. (2008) already reported an increase in neuromuscular jitter, fibrillation potentials and fiber density in the external anal sphincter (EAS).

Postganglionic sympathetic dysfunction affecting epidermal and dermal structures have been reported [Masur et al., 1995; Dettmers et al., 1993]. Furthermore, some groups reported involvement of the peripheral sensory and autonomic nervous system [Bradley et al., 1983; Dyck et al., 1975; Steiner et al., 1984].

Recently, Carvalho et al (2008) concluded, that electrophysiological evidence for chronic neurogenic change plays an important role in ALS.

While new technologies are helping to understand the physiology of the LIS and CLIS and to communicate with these patients, a physiological measurement is needed to evaluate the degree of motor degeneration and physiological changes involved in the above mentioned states.

To investigate the transition between LIS and CLIS, we performed 6 different physiological tests in an ALS patient who went through the above mentioned transition to gain insight into the physiological changes accompanying the transition and to propose the most appropriate approach for a communication system in CLIS, supported by neurophysiological data.

2.5.1. Patient

The patient was a 40 year old end-stage ALS patient. He was diagnosed with ALS in 1997, artificially ventilated since 2000 and entered the CLIS in March 2008. The last successful communication session was through vertical eye movement and was recorded on the 16th of March 2008. The last previous communication mode consisted of a mouth-twitch, therefore we performed electromyography (EMG) experiments in November 2007 to determine if the muscle contractions could be elicited and controlled by the patient but could not produce any response. External sphincter control measurements performed from the 4th of February 2008 onwards were negative. There was, however although rare, weak eye movement control. Vision was severely compromised by necrosis of the cornea due to insufficient fluid availability caused by paralysis and apparent lack of adequate nursing. The patient underwent an epidural electrocorticographic (ECoG) 112 electrode grid and two 5 and 11 electrode strips

implantation over the pre-motor, motor and somatosensory areas in December 2007 in order to guarantee BCI-based communication. Furthermore he suffered from diabetes type II, pneumonia, MRSA colonization, bedsores, and chronic constipation. There were no upper motor neuron degeneration signs (such as spasticity, hyperreflexia/increased tendon reflexes of the lower extremity etc.) indicating no severe affection of the corticospinal tract. We performed three efferent control tests at different days, recording eye, facial and sphincter muscles activity. Three selected brain activity assessment tests are reported. Vibrotactile, auditory and proprioceptive stimuli were used to investigate the integrity and functionality of the different afferent pathways. Motor imagery was used to study self modulated brain activity during LIS and CLIS. The experimental protocol was approved by the ethics committee of the University of Tübingen, Medical Faculty. Informed consent was obtained from the patient and given before entering CLIS and was confirmed several days before the implantation following the protocol described in Section 3 of Haselager et al. (2009). The patient gave consent by signaling "yes" or "no" with vertical eye movements 2 months before he became completely locked in. The sessions with his consent were videotaped and are available on request with the usual legal prerequisites; the following questions were asked repetitively to increase reliability among other personal questions:

Do you wish to continue the experiments with brain wave communication?

Do you want to continue brain communication and life support even if your eye-movements stop in the future?

Do you want to receive electrodes implanted in your brain? (After extensive information by the neurosurgeon).

These questions were repeated 2 days before the operation, but due to the prominent paralysis no significant response pattern emerged. According to German law, informed consent in patients without communication capacity has to be given by the legal representative. In this case a social worker of the responsible hospital was declared legal representative and gave written informed consent to the neurosurgical and experimental procedure.

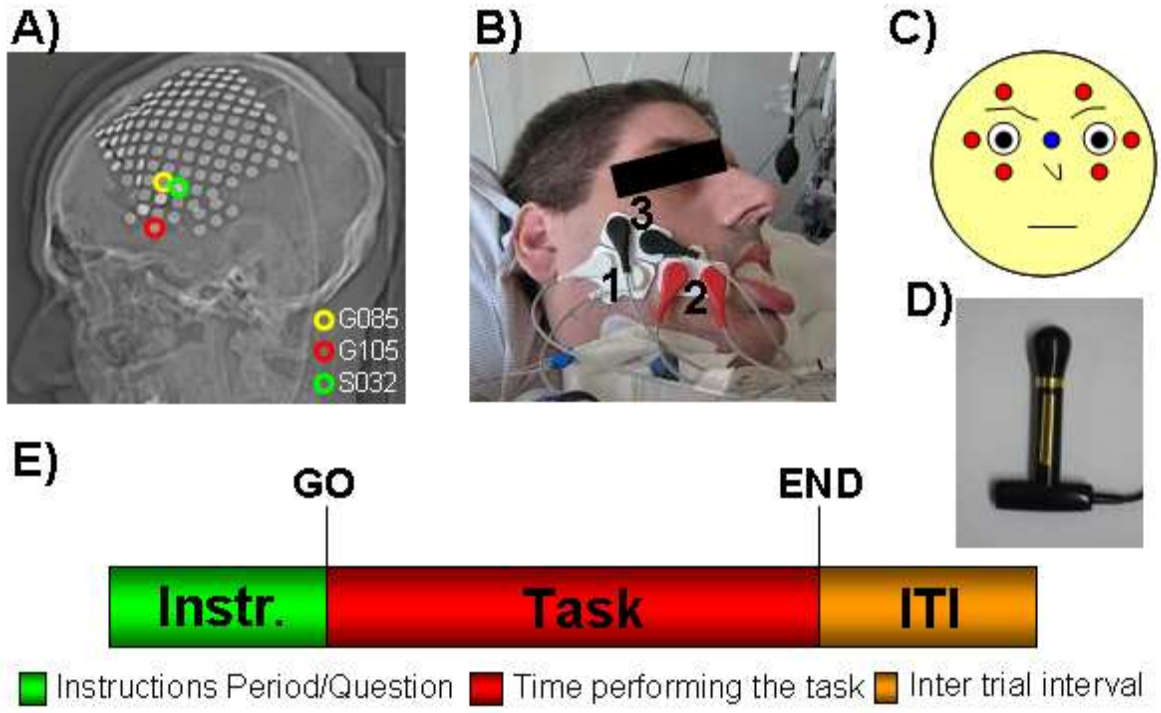

Fig. 22. A) X-ray of patient with the epidurally implanted electrodes. B) EMG electrodes distribution on the face muscles. C) EOG electrodes location. D) External Anal Sphincter Electrode. E) Timing diagram.

2.5.2. Experiment A: Facial Muscle Control

- *Study Design*

Questions with known "yes-no" answers were presented to the patient. After each question the patient had 4 seconds to produce muscle activity around the mouth region in order to answer the questions "yes" and then a Stop cue was presented with an inter-trial interval of 4 sec (Fig 22.E). The patient was asked to do nothing to respond to "No" question. The questions imply a final word that determined the answer maintaining the attention of the patient until the end of the question. An example would be: Is Berlin the capital city of Spain? We performed 3 sessions of 5 runs each. One run implies 12 repetitions of each answer class.

- *Data Acquisition*

Three bipolar Ag/AgCl electrodes from Myotronics-Noromed were used for EMG data acquisition and placed on the risorius muscle and two on the zygomaticus major muscle (See Fig 22.B). The reference electrode was placed over the olecranon and the ground electrode was placed on the clavicle.

Data were acquired using a BrainAmp 32-channel amplifier from Brainproducts GmbH, Munich Germany. Sampling rate was 2500Hz.

- *Signal Processing*

EMG data were filtered between 10 and 500 Hz, rectified and segmented in preselected time windows using the end of the "yes" or "no" question as trigger for the different movement classes. All the segments corresponding to one movement class were concatenated one after the other. Then we separated the EMG data in 200msec windows with 25msec overlap. Four different features that have been extensively used in muscle activity classification [Tenore et al., 2009] were calculated (Mean Absolute Value, Variance Willison Amplitude and Waveform Length). The Waveform Length (WL) feature resulted in higher accuracy for discriminating between classes.The WL of the signal provides both information of the signal amplitude and its frequency expressed within the WL amplitude. It is obtained by the summation of the absolute values given by the difference in amplitude from a point in time (j) with a previous predefined time point (j-1) within a time window.

$$WL = \sum_{j=1}^{N} \left| X_j - X_{j-1} \right|$$

Being X_j the j^{th} point of N points time window of raw EMG.

2.5.3. Experiment B: External Anal Sphincter Control (EAS)

- *Data Acquisition*

It has been demonstrated [Lopez et al., 1999] that there is a strong correlation between surface electrodes applied to the perineal skin and concentric needle electrodes in the diagnosis of anal

sphincter reaction. We used one single bipolar non-invasive anal sensor from Medicheck, Vossbuch, Germany for EAS activity data acquisition (See Fig 22.D).

- *Study Design*

Following the protocol used in the facial muscle control experiment, but the patient was asked to contract the sphincter for YES and relax for NO. During the contraction periods the subject was verbally instructed to maintain contraction and at certain point try to produce a peak in the EMG, to perform a short and intense EAS contraction. The signal was processed as in experiment A.

2.5.4. Experiment C: Eye Movement Control

- *Data Acquisition*

Six monopolar Ag-AgCl sintered electrodes from EASYCAP GmbH, Herrsching-Breitbrunn, Germany were placed following standard physiological landmarks around the eyes for electrooculography (EOG) acquisition. The reference electrode was placed on the patient's nose (See Fig 22.C). Sampling rate was 2500Hz.

- *Study Design*

As in Experiment A, a "yes-no" protocol was selected, using eye movements in a predefined direction (vertical or horizontal) for YES and doing nothing for NO with inter-trial-intervals of 30 seconds and trial duration of 30 seconds. We performed 3 sessions of 5 runs each. One run implies 12 repetitions of each answer class.

2.5.5. Experiment D, E and F: Electrocorticogram (ECoG)

- *Data Acquisition / Instruments*

For experiments D, E and F the signal acquisition was the same. Intracranial brain activity was acquired using a BrainAmp 64-channel amplifier from Brainproducts GmbH, Munich Germany. Sampling rate was set at 500Hz. An epidurally implanted 112 electrode custom made grid from Ad-Tech Medical

Instrument Corporation, Wisconsin, USA was used for electrocorticogram (ECoG) data acquisition (see Fig 22.A) with electrodes S032 and G085 the ground and reference respectively (See Fig. 22.A).

Vibrotactile stimuli were presented using the Quaerosys stimulator, Schotten, Germany. The envelope of the signal was 23-29 Hz with a carrier frequency of 200Hz and duration of touch of 2000 msec.

- *Study Design*

In the passive movement **experiment D** we tried to measure patient's ability to perform motor imagery and his proprioceptive afferent pathways integrity. An auditory stimulus was presented requiring a right foot (dorsoplantar flexion and extension) or right hand movement imagery (hand open and close) in 3 different conditions: motor imagery task without passive movement, motor imagery task with passive movement and passive movement without motor imagery. For the motor imagery condition the patient was instructed to imagine "kinesthetically" the movement as if he was doing it actively. In the conditions with passive movements the hand and foot were extended and flexed passively every 2 seconds. Three seconds after the instruction period indicating hand or foot movement, a GO cue was presented, followed by a 25 seconds task period ending with an END auditory stimulus. If passive movement was requested, the patient limbs were passively moved for the 25 seconds varying between flexion and extension at a 0.5 Hz frequency. There was an inter-trial randomized rest time of 6.5 to 7 sec between the END auditory cue and the beginning of the next instructions period (See Fig 22.E). We performed 3 sessions with 9 runs each. One run implies 15 repetitions of each movement.

In the auditory oddball **experiment E**, 245 standard tones (low pitch) and 45 deviant tones (high pitch) of 100msec duration were presented at 70dB via canal phones with an ITI of 850msec. The patient was instructed to attend to rare, deviant tones.

In the vibrotactile **experiment F** vibrotactile stimulation was applied at three different locations. Right hand index finger tip, right foot big toe tip and the lip were used for stimulator placement. Three different auditory cues representing the 3 anatomical locations of the vibrotactile stimulators were presented to the subject before the actual vibrotactile stimulation. After the cues were presented, the vibration was applied for 12 seconds with an inter trial interval of 10 sec. The patient was instructed to focus his attention towards the stimulated body part.

- *Signal Processing*

In the passive movement **experiment D**, and the vibrotactile experiments F, data were band-pass filtered between 0.5 and 150Hz. The data were transformed into the frequency domain generating 2 Hz frequency bins using the Power Spectral Density (PSD) estimate (Welch's method) with a time window of 500 msec and no overlap. A center-surround local spatial filtering approach, in which a radial difference-of-Gaussians function was used to weight the electrodes at each spatial location, was applied to the ECoG data. After discarding non-functioning channels, the remaining negative weights and positive weights were separately scaled to sum 1, so that the original reference cancelled out. In offline cross-validation experiments, this procedure was found to improve signal-to-noise ratio slightly while ensuring that for each resulting signal, the contribution from electrodes more than one row or column distant was very small. The 25 second trials from experiment D were divided into 5 segments of 5 second windows with no overlap. We calculated the area under the curve (AUC) scores for the comparison between the brain activity in the different conditions and a 3 sec window of the inter-trial-interval used as rest. Hand versus foot brain activity was compared in each condition.

For the auditory oddball experiment E a standard P300 time domain analysis was done averaging over all trials [Polich et al., 1997]. One of the electrodes on the grid was used as reference for the off-line analysis (G105 shown on Figure22.A). We assumed that the distance from this electrode to the auditory cortex enabled a stable reference not influenced by auditory stimuli. The data were downsampled to 100Hz and FIR-bandpassfiltered (order: 500) between 0.5 and 9Hz and cut into 1100msec segments from 100msec before the stimulus presentation to 1000msec afterwards.

- *Results*

Two months before the surgical intervention the patient could still communicate with a twitch of the mouth. This response disappeared slowly but some reflexive movements of his lips could still be observed weeks before the surgery.

The possibility of communication through the mouth twitch was tested every day presenting questions with known "yes-no" answers to the patient and open questions with unknown answers, always with negative results after that date (8th September 2007). Furthermore EMG activity of the previously active muscles was acquired in order to test if any remaining muscle activity was present,

without success. No activity was found using any of the 4 calculated EMG features. Figure 23 presents a comparison between a healthy subject and the ALS patient.

We used a feedforward multilayer perceptrons (MLPs) with varying numbers of hidden layer neurons (empirically chosen to be between 0.5 and 4 times the dimension of the input space) for classifying and testing the facial EMG data of the patient. A classification accuracy of 51% (chance level) was obtained (more information regarding classification process is presented in Tenore, Ramos-Murguialday et al. (2009)).

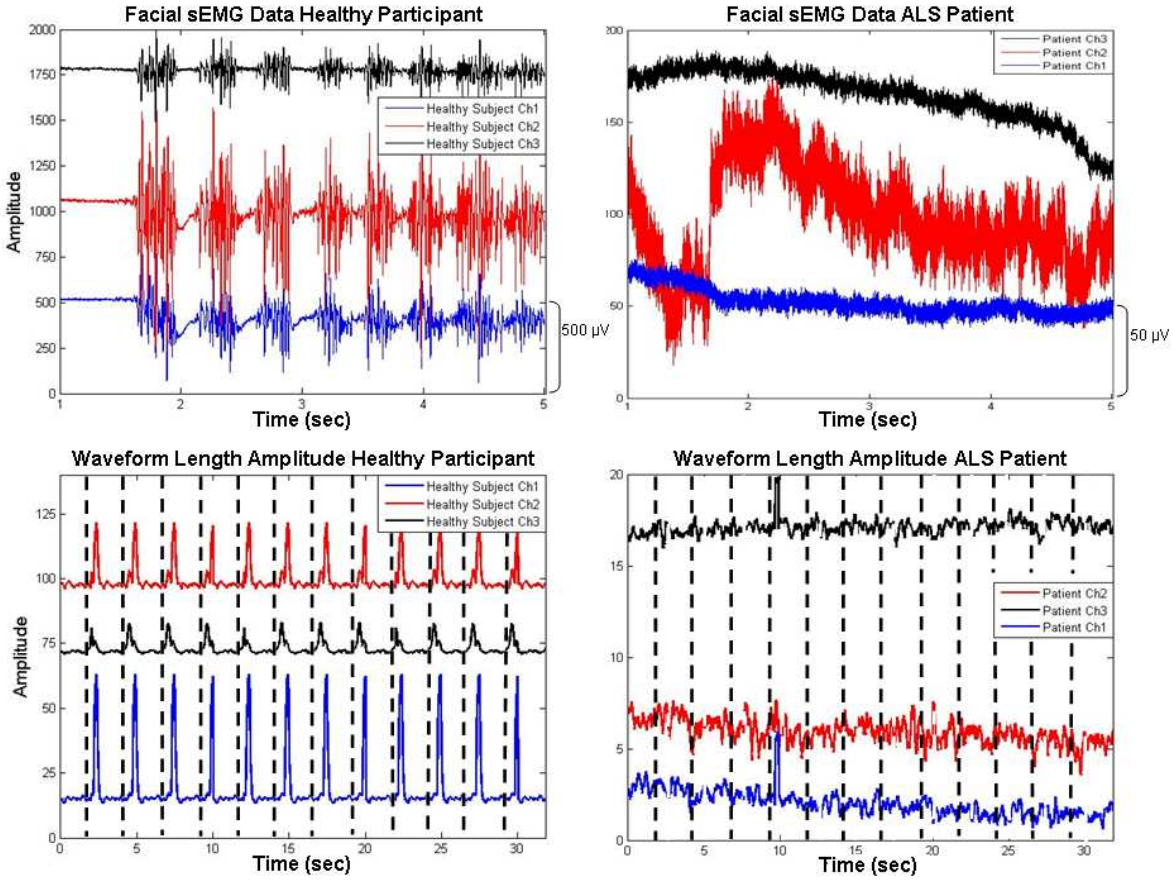

Fig. 23. Facial EMG: On the top representative facial EMG raw activity of the ALS patient in LIS (top right) and a healthy subject (top left) of three different bipolar EMG electrodes (see Fig. 22B) during a "yes" mouth twitch. The bottom plot depicts the waveform length of concatenated trials of the ALS patient (bottom right) and of a control healthy participant (bottom left). The vertical black dashed lines indicate the start of each known YES answer questions in which EMG activity was expected. Please note different amplitude scaling between patient and control.

After the mouth twitch based communication pathway ceased, the eyes appear to be the next suitable option. The patient could communicate with eye movements at two occasions before the

surgery and two occasions after the surgery. This communication pathway was tested every day several times and the EOG was recorded. Figure 24 depicts how the patient was able to move his eyes to answer questions with known answer for a successful session. The red triangles indicate YES answer questions and the black indicate NO answer questions.

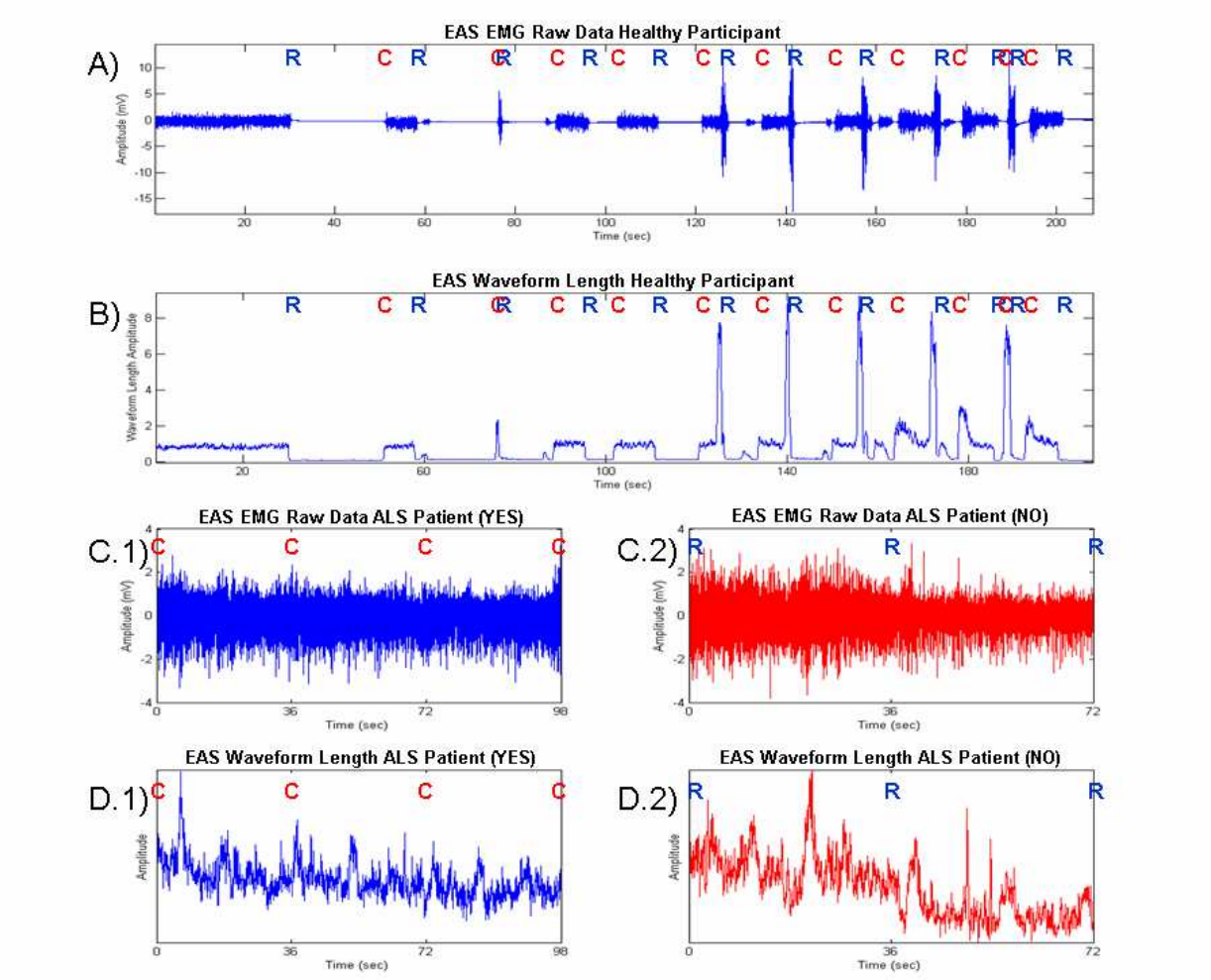

Fig. 24. External Anal Sphincter: A) Raw EAS EMG activity of a healthy person following random auditory triggers. Red "C" indicates (contraction) and blues "R" (relaxation). The high peaks of EMG activity correspond to high intensity contractions. B) WL extracted feature of activity in A. C) Raw EAS EMG signal of the ALS patient and D) WL extracted feature of activity in C. (C.1) and (D.1) "YES" answer trials (contraction) concatenated and (C.2) and (D.2) "NO" answer trials (relaxation) concatenated.

Although the patient suffered fatigue, some days in which the patient could communicate for longer time were recorded until March 2008. In the beginning of February 2008 two EAS experiments were performed, with a week of separation between them. The possibility of remaining anal sphincter control was investigated with negative results. In Figure 25.A and 25.B the raw and transformed EAS data of a healthy person is presented. Red and blue crosses indicate the start and ending of a verbally triggered contraction respectively. A clear difference between rest and EAS contraction is shown. In 4.C and 4.D, concatenated raw and transformed data from the ALS patient for YES (expected EAS activity) and NO (no expected EAS activity) answers is presented. In contrary to the healthy person there is no EAS activity. Corticospinal tract lesions were not visible in MR images from spinal cord excluding the motor neuron degeneration as the most likely cause of the sphincter pathology.

The last communication with the patient took place on the 16th of March 2008. After this date the patient was considered to be in the CLIS. During CLIS we performed somatosensory stimulation in order to test the non visual afferent pathways. In locked-in ALS patients vision is compromised because of lack of adequate eye lubrication and moisture. Many different attempts for BCI communication not reported here were tried during CLIS, all without significant results. During the vibrotactile stimulation (Experiment C) no correlated activity was found in any of the implanted electrodes during any of the stimulations performed on the three different body parts (Index finger, toe and lip). This result is in complete contrast with similar procedures that elicited clear cortical responses in healthy and epilepsy samples [Diesch et al., 2001; Ray et al., 2008; Hansson & Brismar, 1999].

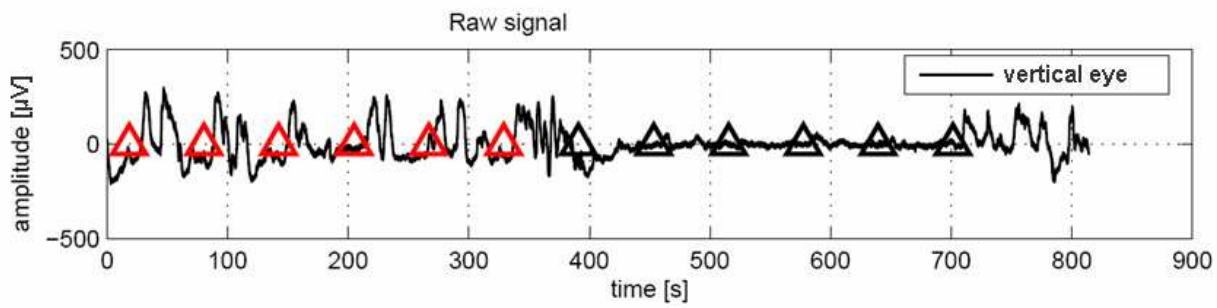

Fig. 25. EOG activity of the ALS patient during LIS. The red triangles were known "YES" answer questions and the black ones known "NO" answer questions. It is important to note that the EOG was clearly correlated with the presented cues at the beginning of the session.

Nevertheless, while passive movements were performed on patient's foot and hand, activation of the somatosensory cortex was detected with and without simultaneous motor imagery task. The

statistical analysis was performed, following [Agarwal et al., 2005] on the area under the curve (AUC) values, comparing hand versus foot, hand versus rest and foot versus rest from the ECoG data within the frequency domain focusing on motor imagery, passive movements and both simultaneously. We found statistically significant values ($p < 0.05$) while comparing hand versus foot passive movements and hand passive movements versus rest in specific frequency bins during LIS and in CLIS but no significant results were found for the foot versus rest conditions.

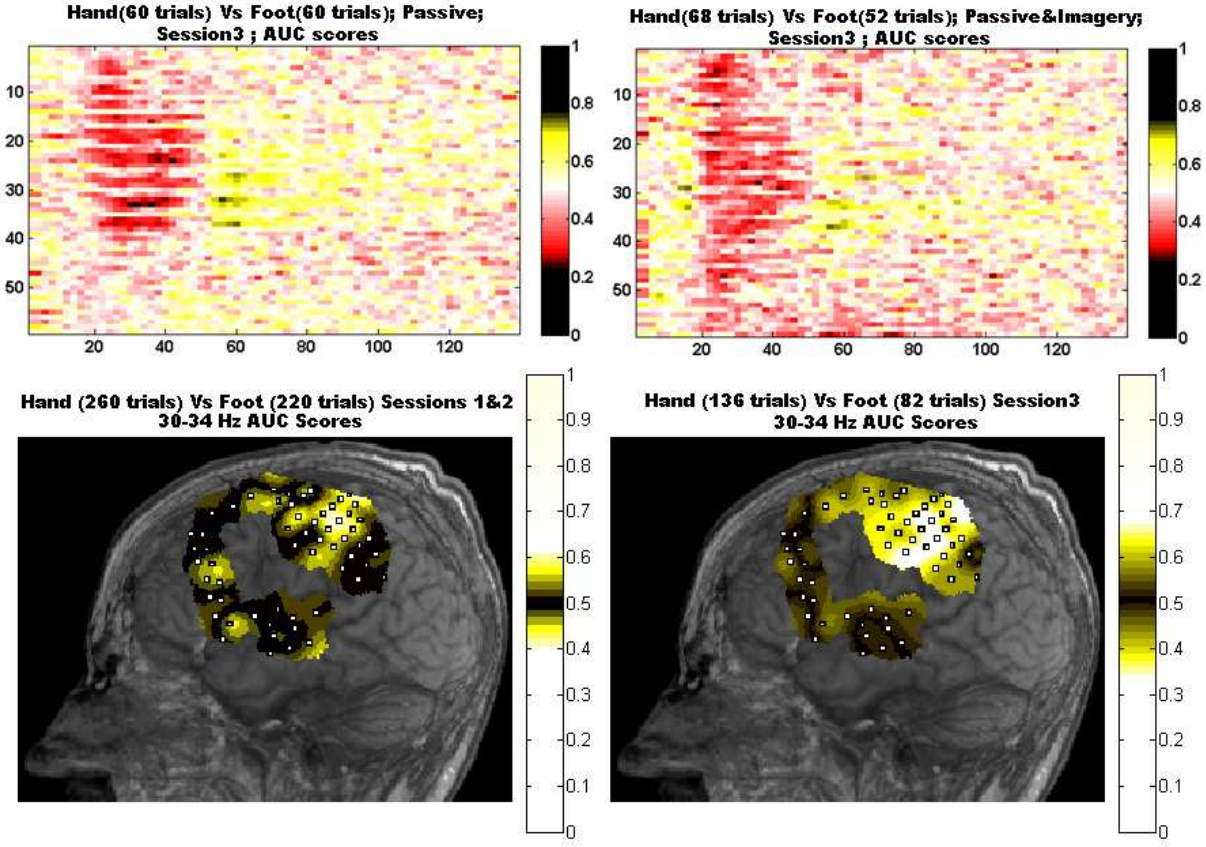

Fig. 26. ECoG activity during passive movement: On the top area under the curve (AUC) scores comparing foot versus hand movements of Session 3 (CLIS); On the left side passive movements alone and on the right passive movements and motor imagery simultaneously AUC scores. In black the values that are statistically significant comparing hand versus foot movements. At the bottom the AUC scores in the frequency bin from 30 to 34 Hz plotted on the ALS patient X-Rays (left, sessions 1&2 LIS and right, session3 CLIS) comparing hand versus foot passive movements. In white the statistically significant AUC values. The hole in the center of the electrode grid is due to high impedances or lost channels.

Comparing foot versus hand passive movement cortical activity, significant results at 30 and 40 Hz frequency range were found in all the sessions and at 20Hz frequency range for the simultaneous passive and imagery condition, while for the comparison hand versus rest, the significant activity was at 20 and 40 Hz frequency range for passive movements and at 40Hz frequency range for passive

movement and simultaneous motor imagery. No significant values where found for the comparisons during motor imagery only. However, when all the trials with passive movement were analyzed independent of being accompanied by imagery or not, AUC statistical analysis showed the significant frequencies during both LIS and CLIS to be at 20Hz frequency range for Foot versus Hand and at 40 and 60 Hz frequency range for Hand versus rest. (See Table 2)

The electrodes showing high correlation with neural activity were located on the hand somatosensory area (See Fig.26).

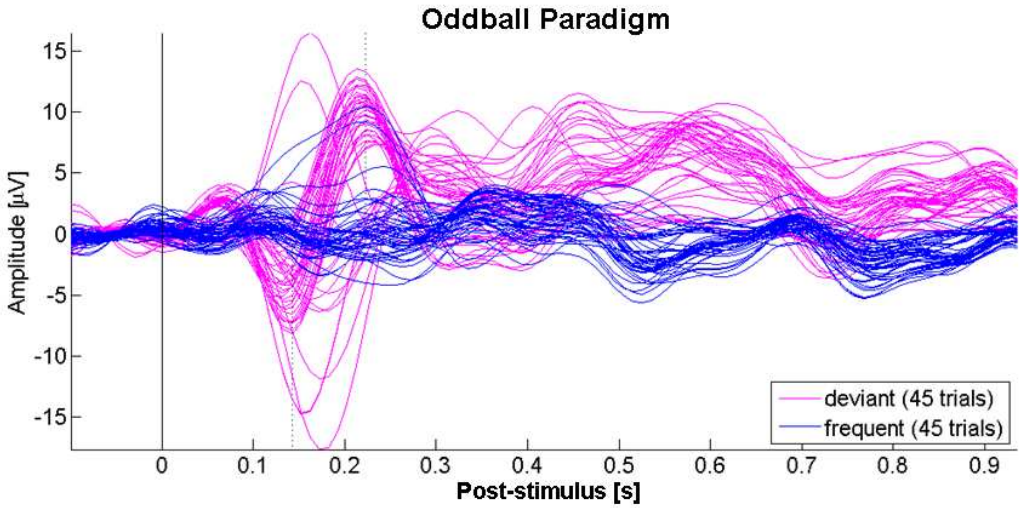

Fig. 27. Averaged Auditory evoked ERPs during CLIS for 45 standard (blue) and deviant (magenta) tones. Each line represents one ECoG grid electrode recording. The vertical black line indicates beginning of the stimulus (Time=0 sec).

During the auditory oddball paradigm, two days after entering the CLIS state, clear averaged brain activity was detected. Shown in Fig. 27 are the averaged ERPs for 45 standard (blue) and deviant (magenta) tones from one representative run. Each line represents one of the 48 non-artefacted recording channels of the ECoG grid, re-referenced to another common grid channel (See Fig.22.A G-105). The figure shows the N1/P2 component for the deviants, as well as the delayed P300 response in the range of 400-700msec. These results demonstrate intact afferent auditory pathways and automatic attention, even though the N1/P2 complex is not clearly visible for the standard tones.

- *Discussion and Conclusion*

LIS-CLIS transition was analyzed in one patient with ALS in several neurophysiological experiments that should provide information about the different stages of this nervous system disorder. Between LIS and CLIS there are some clear physiological differences. Although the data presented in this paper are from one single patient only, who underwent the LIS-CLIS transition, this data set is unique and could be used as a first step towards a physiological data based instrument to define end stages of ALS and probably some other neurological diseases.

In the present patient the last remaining controllable muscles were the eye muscles. This contradicts the hypothesis that the external anal sphincter is the last remaining controllable muscle in ALS. Jokelainen and Palo (1976) found no reports of rectal or bladder dysfunction in their review of 300 ALS patients. But it was also reported that this muscle is affected by the disease [Carvalho et al., 1995; Pullen & Martin 1995; Xu et al., 2007; Palmowski et al., 1995; Balaratnam et al., 2010] but we have not found any publication reporting the complete extinction of eye and sphincter movement control as observed in the present patient.

The fact that there is no cortical activation during vibrotactile stimulation may indicate that skin mechanoreceptors information is not reaching the cortical areas or that the skin mechanoreceptors do not function properly, at least in response to moderate to medium stimulus intensities. In contrast, proprioceptive information is processed in the brain as shown in the passive movement experiments. We hypothesize that joint receptors and muscle mechanoreceptors are less affected by the consequences of long-term immobilization than skin mechanoreceptors. Skin mechanoreceptors are located more at the body surface and therefore being more susceptible to damage from atrophy and skin deformation. These data suggest that muscle mechanoreceptors or joint receptors degenerate later than the skin mechanoreceptors and that at least some of the group Ia, II and Ib afferent fibers, muscle spindles and Golgi tendon organs are preserved in the CLIS. It has been proposed that joint receptor afferent input to the brain might be only significant when muscle spindle afferents do not contribute to proprioception [Burke et al., 1988]. Taken together, the data indicate that if the above mentioned mechanoreceptors are not preserved then some of the joint receptors such as Ruffini endings, Pacinian endings and Golgi tendons and their respective fibers (slow and fast adapting fibers type II) should be preserved. On the other hand, the slowly adapting fibers type I and II (SAI and SAII), fast adapting type I and II (FAI and FAII) or their corresponding receptor types (Merkel cell, Ruffini ending, Meissners corpuscle and Pacinian ending respectively) may be affected in CLIS.

Auditory information processing is preserved. Motor imagery did not elicit statistically significant brain activity when compared to rest. However, when motor imagery was performed accompanied by passive movements, the statistically significant frequency range obtained was different from the one obtained when passive movements without imagery were compared to rest. The classified activity decreased and shifted towards lower frequencies suggesting that some motor imagery might happen in CLIS.

We tried visual BCIs as described in Nijboer et al. (2008b) without success.

Due to eye infection and to the ECoG location visual experiments were not performed after implantation. Due to the paralysis of eye-muscles in end stage ALS, vision is severely compromised due to dryness of the cornea. The cornea of our patient was already seriously damaged months before the implantation, thus, significant results from visual experiments were not expected.

We believe that the reduced sensory information flow could play an important role in the extinction of motor imagery ability necessary for some BCI based communication in CLIS as proposed by Kübler and Birbaumer (2008). Furthermore, the modality of elected BCI communication should consider the few remaining afferent flow information to avoid lack of feedback and thereby the above mentioned "extinction of thought" problem.

Kotchoubey et al. reported that all CLIS patients of the sample reported in [Kübler & Birbaumer, 2008] had normal ERP-responses to one or more of the complex cognitive tasks, indicating at least partially intact cognitive processing in LIS [Hinterberger et al., 2005b] and CLIS [Kotchoubey, 2005]. We may conclude that somatosensory and visual processing is not intact in CLIS and the complete lack of motor control and lack of all kind of contingent external feedback for behavioral responses might be responsible for the cessation of voluntary cognitive activity and intention, goal directed thinking and imagery.

Since communication through a BCI seems to be the only way to avoid the extinction of thought it is necessary to know which afferent pathways would be more appropriate for feedback and reward. From these data reported here we conclude that passive movement or auditory based BCI are the only remaining possibilities. Other ways of afferent stimulation using nociceptors (pain receptors) and invasive stimulation is ethically problematic. Temperature stimulation or pH-communication (105) could be another option and should be considered. Sniffing is not possible because it needs somato-muscular

control. SCR regulation is not possible because of complete cessation of SCR in many if not in all ALS patients.

The last observed controllable muscle besides eye muscles may vary between persons and usually involves facial muscles. The EAS is affected by the disease [Carvalho et al., 1995; Xu et al., 2007] and in spite of some fibrillation, no reliable control was possible. Once eye movements are lost the patient has reached the CLIS. In this state atrophy impairs mechanoreception of the skin while the auditory and muscle joint receptors pathways remain intact eliciting some cortical responses. BCI-based communication with auditory [Nijboer et al., 2008a] and visual stimulation as described by our group [Nijboer et al., 2008b] or imagery [Kübler & Birbaumer, 2008] did not result in reliable communication in CLIS. The fact that the auditory and proprioceptive systems still elicit brain responses suggests that BCI platforms for LIS and CLIS patients should avoid using feedback strategies that use visual or mechanoreceptive systems, and focus on disease-resistant systems such as auditory or proprioceptive systems that could be used in the LIS-CLIS transition. This might be the only way to prevent the "extinction of thought" in CLIS patients.

Table 2. Statistically significant frequency bins obtained from the area under the curve (AUC) analysis performed in the LIS (Sessions 1&2) and CLIS (Session3) comparing different conditions. Passive stands for passive movement alone of the patients hand or foot, Passive&Imag stands for passive movement while the patient was asked to imagine the same movement and Pass&Imag+Pass stands for all the trials in which the patient's limb was passively moved independently of simultaneous imagery or not. Please note the stability of the statistically significant frequency ranges in the different conditions during locked-in state and completely locked-in state.

	Session 1&2 Freq. Bins (Hz) LIS	Session 3 Freq. Bins (Hz) CLIS
Foot Versus Hand Pass&Imag	16 to 20 Hz	20 to 24 Hz 36 to 38 Hz
Foot Versus Hand Pass&Imag+Pass	16 to 22 Hz and 30 to 32 Hz	20 to 42 Hz 60 to 62 Hz and 70 to 72 Hz
Foot Vs Hand Passive	32 to 36 Hz and 40 to 42 Hz	29 to 36 and 40 to 42Hz 56 to 58 Hz
Hand Versus Rest Pass&Imag	6 to 8 Hz 40 to 42 Hz and 60 to 62 Hz	22 to 26 Hz 38 to 40 Hz
Hand Versus Rest Pass&Imag+Pass	6 to 8 Hz 40 to 46 Hz 60 to 86 Hz and 92 to 94 Hz	20 to 26 Hz and 30 to 34 Hz 40 to 44 Hz 60 to 66 Hz
Hand Versus Rest Passive	24 to 26 Hz 40 to 42 Hz 74 to 76 and 84 to 86 Hz	22 to 28 Hz 40 to 44 Hz 58 to 60 Hz

3. **Darstellung des Eigenanteils** bei Gemeinschaftsarbeiten (Publikationen):

Birbaumer N, **Ramos Murguialday A** and Cohen L. *Brain-Computer-Interface (BCI) in paralysis*. In: Current opininon in Neurology, 2008. Vol. 21(6):634-638.

In this work I did a literature review and helped writing the manuscript.

Chatterjee A, Aggarwal V, **Ramos Murguialday A**, Acharya S, and Thakor NV. *A brain-computer interface with vibrotactile biofeedback for haptic information*. J. NeuroEngineering and Rehabilitation 2007, 4:40.

In this paper I acquired the data and did the protocol design, the EEG signal processing and helped writing the final manuscript.

Escolano C, **Ramos Murguialday A**, Matuz T, Birbaumer N, Minguez J. *A telepresence robotic system operated with a P300-based brain-computer interface: Initial tests with ALS patients*. Engineering in Medicine and Biology Society (EMBC) Proceedings, 2010 Annual International Conference of the IEEE 2010 page(s): 4476 – 4480.

In this study I acquired the data, designed the protocol of the experiment and contributed writing the final manuscript.

Gu Y, Farina D, **Ramos Murguialday A**, Dremstrup K, Montoya P, Birbaumer N. *Offline identification of imagined speed of wrist movements in paralyzed ALS patients from single-trial EEG*. Frontiers in Neuroprosthetics 2009. doi 10.3389.

In this work I contributed in the design of the experiments and writing the manuscript.

Hoffmann U, Cho W, **Ramos-Murguialday A** and Keller T; *Detection and removal of stimulation artefacts in electroencephalogram recordings*. Engineering in Medicine and Biology Society (EMBC) Proceedings, 2011 Annual International Conference of the IEEE 2011 (InPress)

In this publication I contributed in the experimental design and writing the manuscript.

Ramos Murguialday A, Halder S, and Birbaumer N. *Propioceptive Feedback in BCI*. In proceedings of NER'09, 4th International IEEE EMBS Conference on Neural Engineering, Antalya, Turkey, 2009.

In this work I designed the experimental protocol, acquired the data, analyzed the data and wrote the manuscript.

Ramos Murguialday A; Soares E; Birbaumer N; *Upper Limb EMG Artefact Rejection in Motor Sensitive BCIs*; Engineering in Medicine and Biology Society (EMBC) Proceedings, 2010 Annual International Conference of the IEEE 2010 page(s):1 - 6

In this work I designed the experimental protocol, acquired the data, analyzed the data and wrote the manuscript.

Ramos Murguialday A, Hill J, Bensch M, Martens S, Halder S, Nijboer F, Schoelkopf B, Birbaumer N, Gharabaghi A. *Transition from the locked in to the completely locked-in state: a physiological analysis*. Clin Neurophysiol. 2011 May;122(5):925-33. Epub 2010 Dec 9.

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S. Silvoni, **Ramos-Murguialday A**, Cavinato M, Volpato C, Cisotto G, Birbaumer N and Piccione F*; BCI in Srtoke: a review of Progress*; IEEE Journal of Neuroengineering and Rehabilitation; 2011; (Under Review)

In this publication contributed in the writing of the manuscript and literature gathering.

Tenore F, **Ramos Murguialday A**, Fahmy A, Acharya S, Etienne-Cummings R, and Thakor NV. *Decoding of individuated finger movements using surface Electromyography*. In: IEEE Transactions on Biomedical Engineering 2009. 56(5):1427-34.

In this paper I designed the experimental protocol, acquired the data, analyzed the data and wrote the manuscript.

Caria A, Weber C, Brötz D, **Ramos Murguialday A**, Ticini LF, Gharbaghi A, Braun C, Birbaumer N. *Chronic stroke recovery after combined BCI training and physiotherapy*. A case report. Psychophysiology 2011; 48: 578-582.

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