## MSc Thesis

## Corticomuscular communication study by using current source density analysis



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### Preface

On the introductory day of my master progam, a demonstration of the master thesis of Ricardo Ruiz Torres was held in the Schoulder Lab of the Biomedical Engineering Department of TU Delft. In his thesis, Mr.Torres examined the nature of corticomuscular communication through an experiment of perturbation of the finger. I got immediately interested on the field of motor control and specifically on the role that the brain has in it. I therefore contacted his supervisors, Dr. F.C.T. van der Helm and Dr. A.C. Schouten, to whom I expressed my will to do a research in a form of a master thesis in the regions of the brain that may contribute to motor control. As a first step of this project, I did a literature survey on the factors that affect the accuracy of the spatial resolution of electroencephalography (EEG), which was the tool through which it was decided to study the brain activity during a motor control task. Subsequently, Dr.van der Helm arranged for me an internship in eemagine Medical Imaging Solution office of the company ANT in Berlin, Germany where I had the chance to be involved into the whole procedure of designing and constructing an EEG system, being associated with the software development of an innovative EEG amplifier. As a final step, an experiment was arranged with the help of Dr. A.C. Schouten in the Experimental Centre of Technical Medicine at the University of Twente and performed with the help of S.F. Campfens, MSc who is a PhD student in the latter university. The analysis of the data acquired through this experiment is presented in this report. I am intending to publish the results of my master thesis in Biological Cybernetics, an interdisciplinary medium for experimental, theoretical and application-oriented aspects of information processing in organisms, including sensory, motor, cognitive, and ecological phenomena.

# Corticomuscular communication study by using current source density analysis

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Abstract- Corticomuscular communication during wrist motor tasks was investigated in this study. EEG signals from the sensorimotor cortex and EMG data from the reflexive carpi radialis and extensor carpi radialis muscles were recorded from five healthy subjects while performing visual-motor force tasks, with and without perturbation on the wrist. Different continuous perturbation signals with different frequency content (multisines), as well as perturbation resulting in rapid angular displacements of the wrist were applied to study the existence of synchronization on corticomuscular communication, as well as the possible trancortical contribution to the late reflexes on the muscle. Corticomuscular, perturbation- EEG and perturbation -EMG coherences were calculated for all tasks. Three out of five subjects did show high coherence results in beta band when applying multisine perturbation and decreased in base task and in tasks with rapid angular displacements of the wrist, implying an Ia afferent contribution from muscle spindles to beta EEG. The connection of the perturbation to the brain and the muscles is considered non-linear due to high corticomuscular coherence found in harmonics of the excited frequencies. Current source density was applied on frequencies with high corticomuscular coherence. Contralateral supplementary motor cortex is more likely to cause corticomuscular communication at high frequencies of the beta band. Moreover, proprioceptive-evoked potentials were calculated from tasks with continuous rapid angular displacements of the wrist. The basal ganglia is more likely to be involved in the generation of early proprioceptiveevoked activity.

*Index Terms*—Continuous perturbation, current source density ,DICS, dipole fitting, EEG, EMG, head model, multisine, wrist.

Manuscript received (will be inserted by the editor).

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#### I. INTRODUCTION

Different Different parts of the central nervous system (CNS) contribute to voluntary movements. Fast reflexes mainly involve a spinal pathway, while for more complex and planned movements in particular, the basal ganglia and the motor cortex are included. From a clinical perspective, understanding of the cortical involvement in motor control is an important issue in integrative neuroscience. The relation between the cortex and the musculoskeletal system will be beneficial in the understanding and diagnosis of several movement disorders, which are caused by degeneration of the CNS, such as Parkinson's disease, cerebrovascular accidents, spasticity or dystonia.

Involvement of the cortex in motor control can be studied by using proprioceptive stimuli, which can be a change in joint angle or a change in the torque. Proprioceptive input can be generated by two different ways: by electric stimulation of a nerve, as well as by applying some kind of mechanical perturbation signal (transient or continuous) on a device, such as a manipulandum, that the subject has to control. Neuromuscular properties are then derived from the analysis of the response in time and frequency domain.

Time domain analysis of EEG responses to proprioceptive stimuli has shown that these stimuli elicit evoked potentials that can be recorded in EEG: proprioceptive evoked potentials (PEP) [1, 17, 18]. These potentials have been associated with reflexive responses in the muscles during an involuntary muscle stretch [1, 20] and specifically with the long latency stretch response (LLSR). LLSR is the second component of muscle reflexes, the first being a rapid muscle contraction referred to as short-latency stretch response (SLSR). Both SLSR and LLSR can be identified in the early activity of EMG, before volitional one, which starts approximately 100 ms after the onset of the stimulus [2]. Their timings, referred to as M1 and M2, have been defined at 20 to 45 ms and at 45 ms (60 ms in case of the wrist [1]) for SLSR and LLSR respectively [3].

In contrast to M1 which is a monosynaptic stretch reflex, mediated by group Ia afferents from muscle spindles of the stretched muscle and is of spinal origin, the origins of M2 is still the subject of considerable controversy, as being a flexible reflex that can be modulated separately from the M1 [4]. M1 is modulated by the change in the length of the stretched muscle, as well as by the velocity of the stretch [5], whereas for M2 is assumed to be the result of either the of either the contribution of slower afferents, like group II afferents [6, 7], or of cutaneous afferents [8] or even that is has a supraspinal origins [1, 9, 10]. The latter is gaining more and more acceptance, with several authors arguing that M2 evoked in the distal musculature of the upper limb is predominantly mediated by a transcortical pathway through the contralateral primary motor cortex. Described PEP around 55 ms following the muscle stretch due to wrist extension led to the conclusion that this evoked activity is directly related to the LLSR transcortical loop [1, 17]. It has been also proved that task instruction plays an important role in modulation of the M2 response. Depending on whether the subject resists the stretch perturbation or not, EMG activity in the M2 window was suppressed or enhanced respectively [11, 12].

Furthermore, in a study with simultaneous measurement of EEG and EMG in response to proprioceptive stimuli, the PEP precedes the M2 and it modulates together with the long latency reflex when a subject receives a different task instruction [1]. However, in a study on patients with Huntington's disease who lacked an M2 in the first dorsal interosseus, the patients showed normal biceps brachii, triceps brachii, and triceps surae M2 responses, suggesting that the M2 response was not invariably mediated over supraspinal pathways [13], indicating that trans-cortical contributions are at least not universal to all muscles.

Besides PEP studies, several electrophysiological studies have shown that under specific conditions, the signals recorded from brain and muscle activity are synchronized, implying a functional connection between these structures. The synchronization of the signals is expressed by the corticomuscular coherence (CMC) [14, 15]. CMC is a measure for the linear relation between the EEG and EMG signals expressed in the frequency domain. It is a normalized value, which ranges from 0 to 1, where the higher the value, the more linearly related the signals are. In the frequency points in which high coherence is observed, the time delay and transfer function between the two signals can be reliably estimated. CMC in the beta range (15 - 30 Hz) has been hypothesized to underlie a mechanism through which the cortex is able to achieve fine motor control [14, 16]. CMC during isometric muscle contractions was demonstrated by non-invasive EEG recordings [7, 19] in healthy subjects and confirmed with intracortical local field potential (LFP) recordings in monkeys [14].

CMC in beta band is reduced prior to and during a movement and appears predominantly during periods of isometric contraction following the movement [2, 21] and reaches its maximum peak in the beta frequency range over the primary sensorimotor cortices contralateral to the perturbed

limb [22]. Across studies CMC magnitude ranges between 0.02 and 0.2 [21, 23]. In the beta band, CMC peak frequency, spectral distribution and magnitude show task, attention and age related modulations, with accompanying behavioral consequences [21, 24]. CMC has also been found in the mu band (8 to 12 Hz) [25], as well as around 40Hz (gamma band) during strong and oscillatory contractions control [26]. Consequently, the study of corticomuscular coherence in motor control is relevant as it can provide us with the information on which structures are communicating, improving by this way the understanding of the circuits involved in the generation of motions.

Both PEP and CMC measures show downsides. First, even if CMC consists of a sign of corticomuscular communication, it does not provide us with any information on the direction of this communication, meaning that it is not possible to distinguish whether afferent or efferent pathways contribute to it, when it is most likely generated by a combination of both. Therefore, it is difficult to interpret the functional role of CMC. On the other hand, the current methodology of PEP analysis is limited by the large number of repetitions of the proprioceptive stimulus needed in order the noise to be removed by averaging over a number of trials. Since proprioceptive input is always in a form of discrete pulses, these protocols are considered as very time consuming and therefore the investigation of the influence of different parameters of the perturbation such as velocity and amplitude is limited. There is no study so far that has tried the use of continuous perturbations as proprioceptive input.

Moreover, another limitation in the examination of corticomuscular coupling is the limitation in the interpretation of EEG responses, since EEG is strongly depended on the choice of the recording reference. Most of the times, a non-cortical site is preferred (e.g. mastoid, earlobe, nasion) so as to eliminate sacrificing a site of interest, when nowadays EEG recordings are referenced online on the average over the whole electrode montage, the so-called common average reference (CAR). Under some assumptions, the CAR results in a spatial voltage distribution with a mean of zero, providing EEG recording that is nearly reference free [29]. Even CAR though is not immune to the reference problem.

The reference problem is more evident when the EEG is quantified using power spectra [27] which may suffer topographic distortion or the reversal of hemispheric asymmetries (e.g. in [28]). Therefore, the theoretical rationale regarding the nature of the underlying activity in the brain should be taken into account. Finding the neuronal generators of the recorded EEG consists of solving the inverse EEG problem, which is implemented by the use of the current source density (CSD), a reference-independent measure of the strength of extracellular current generators underlying the grossly recorded EEG that is firmly based on a linear volume conduction model [30]. The fidelity of CSD depends on the spatial scale of the physical model. At the lowest scale, that is, on the level of scalp-recorded EEG topographies, surface Laplacian CSD estimates are indices of radial current flow into the skull from (normal to) the underlying neural tissue (i.e. radial current flow; [31, 32, 35]), for the relationship between the surface Laplacian and the normal derivative of the potential gradient). At the next, intermediate scale, the same topographies may be described using inverse models to extract intracranial generators (e.g. equivalent current dipoles, [36]; LORETA, [34]). Finally, at a microscopic scale, CSD profiles can image sublaminar sources and sinks, but for this intracranial recording are required which limits the application to animal experimental studies.

The goal of this project is to understand the mechanisms of corticomuscular communication; corticomuscular communication is expressed either as a contribution of identified PEP in the generation of LLSR or as high CMC in different EEG bands. We therefore wanted to localize the underlying sources in the brain that are excited by proprioceptive input and contribute to the recorded muscle activation.

To overcome the afore-mentioned drawbacks of the existing techniques, we explore the use of system identification techniques. System identification considers the system under investigation as a black box and tries to discover different characteristics of the system by carefully choosing input signals (perturbations) and analyzing the systems response to these inputs. The use of perturbations can overcome the problem with causality in a closed loop system by relating all signals to this independent input signal. By choosing the properties of the input signal, different signals can be generated suitable for highlighting different aspects of the systems.

Furthermore, we examined the use of surface, as well as intracranial CSD, in order to improve the spatial resolution of EEG. We want to localize the regions in the brain that may contribute to CMC. A method called DICS (Dynamic Imaging of Coherent Sources) from the Fieldtrip Matlab toolbox is used to achieve that. DICS has been used with great success in several studies that identified coherent networks of brain regions involved in motor activity, both in healthy subjects and in patients with movement disorders [37, 38]. Moreover, we applied dipole fitting to identify the EEG sources modeled as dipoles in the brain that explain better the recorded EEG topography during the early cortical activity. By comparing the corresponding timing of the LLSR in EMG, we can conclude whether the identified PEP contribute or not to the generation of EMG reflexes. For both the afore-mentioned intracranial CSD approaches, a head model is required. Two different head models are applied, one spherical and one realistically shaped in which a triangulated mesh is created in every surface

between the different tissues of the head by the use of Boundary Element Model (BEM).

To this end, a muscle stretch experiment on the flexor carpi radialis was performed, in which EEG and EMG were recorded by electrodes on the scalp and the low arm respectively. Previous studies reported that the coherence was higher when the task involved an isotonic condition rather than an isometric condition [2, 21]. Therefore the task of the experiment was a force task, where the subject had to maintain a constant force on the manipulandum, with position deviations as input. Two different perturbations of different shape and frequency content were used. For the use within frequency domain identification perturbations were designed with specific frequency contents that cover the alpha, mu and beta band of the EEG power spectrum (5 – 30 Hz). For the use within time domain identification perturbations were designed with specific autocorrelation properties.

The choice of wrist tasks for this project is due to the large cortical area devoted to digit control [63], which facilitates the measurement of electrical signals originating there. Moreover, the wrist receives strong direct control from the motor cortex, which increases the chances of showing a transcortical pathway for M2, in contrast to other joints of the arm [13]. The main muscle in charge of wrist flexion is the flexor carpi radialis (FCR), while the extensor carpi radialis (ECR) plays a secondary role in this task, being specialized in wrist abduction. Activity from both muscles will be compared with activity from the area representing the lower arm in the sensorimotor cortex, as well as with the location of the sources justifying the recorded EEG on this region of the cortex.

In summary, the questions that are intended to be answered are the following:

- Is there a synchronization between the brain's and the muscles' activation and in which frequency band? Is this relation linear or not?
- Is there an evident causality between the electrophysiological signals EEG and EMG?
- Which region of the cortex is active in the frequencies that CMC is present?
- Can a continuous proprioceptive stimulus still result in an early cortical response that may contribute to the generation of the late reflexes in EMG?
- If so, can a region in the brain be localized that may explain this early cortical response?



Top view diagram of the human head showing EEG electrode locations. The lines starting at CPz represent the approximate location of the central sulcus (fold in the cortex frontal to the somatosensory cortex and posterior to the motor cortex)

#### II. METHODS AND MATERIALS

#### A. Subjects

The experiment took place at the Experimental Center of Technical Medicine at the University of Twente. Five healthy subjects (age range 26-30 years) participated voluntarily in the study, after giving informed written consent prior to the experimental procedure. The dominant hand was determined using the Dutch Handedness Questionnaire [39]. All subjects were right hand dominant and had no history of injury of the arm or neurological disorders.

#### B. Experimental setup

The manipulandum that was used to apply perturbation to the wrist the input stimulation is called Wristalyzer (Moog, Nieuw-Vennep, The Netherlands). An arm support was used in order to restrain the lower arm of the subject. The manipulandum and the arm rest can be turned such that movement is in the horizontal plane. For the acquisition of the EEG, EOG and EMG signals, the Refa System from TMS (Twente Medical Systems International) was used, which is a multi-channel amplifier system for stationary use. EEG scalp recordings were obtained from a montage of 64 gold-disk electrodes placed on the surface of the scalp .sites including:Fp1,Fp2,Fp2,F7,F3,Fz,F4,F8,FC5,FC1,FC2,FC6,M1 ,T7,C3,Cz,C4,T8,M2,CP5,CP1,CP2,CP6,P7,P3,Pz,P4,P8,POz



Subject 1 wearing the EEG cap with the EEG electrodes attached on it, holding the handle of the manipulator. The EOG and EMG electrodes which are attached on the head and right arm respectively can be seen too.

,O1,,Oz,O2,AF7,AF3,AF4,AF8,F5,F1,F2,F6,FC3,FC2,FC4,C5 ,C1,C2,C6,CP3,CPz,CP4,P5,P1,P2,P6,PO5,PO3,PO4,PO6,FT 7,FT8,TP7,TP8,PO7,PO8. The electrodes were positioned according to Oostenveld's 10-10 system [54] in the locations shown in Figure 1. M1 and M2 electrodes are placed on the left and right mastoid respectively. All electrodes were filled with conductive gel to ensure a good signal to noise ratio. Scalp/electrode impedance was kept below 5 k $\Omega$ . All EEG signals were differentially amplified with respect to an average reference. To monitor eye movement and detect eye blinks, two extra Ag/AgCl electrodes were placed above and below the right eye, creating a bipolar EOG channel. For the EMG measurements, pairs of Ag/AgCl electrodes were placed 2 cm apart, over the muscle bellies of the m. flexor carpi radialis (FCR) and the m. extensor carpi radialis (ECR) of the dominant arm and differentially amplified. All signals were sampled at 2048 Hz using the data- acquisition software (ANT ASA signal & source analysis package). All channels of EEG and EMG are amplified against the average of all respective connected inputs, whereas for EOG, two sensors were used with bipolar reference, so signals from each electrode are differentially lined to each other. The manipulator's handle together with the setup of all the electrodes used in the experiment can be seen in Figure 2.

| Stimulus  | Amplitude (mA) | Peak-to-peak<br>transition angle | Feature                                | Duration | No. of repetitions    |
|-----------|----------------|----------------------------------|--|----------|-----------------------|
| Base task | -              | -                                | -                                      | 60       | 6                     |
| MS1       | 1              | 3°                               | Frequency (Hz) : 5,9,13,17,21,25,29    | 55       | 7 (14 for subject 1)  |
| MS2       | 1              | 3°                               | Frequency (Hz) : 5,7,11,13,17,19,23,29 | 55       | 7 (14 for subject 1)  |
| PRBS1     | 1              | 1°                               | Stretch velocity (%) : 120             | 62       | 10 (20 for subject 1) |

 1
 Image: Stretch velocity (°/sec) : 120
 62
 10 (20 for subject 1)

 Stimulus : kind of stimulus. Peak-to-peak transition angle: maximum angle disposition of of the handle of manipulator due to the stimulus.

Feature: contained frequencies for multisines and value of stretch velocity for PRBS1., Durations of each trial in each task.

No.of repetitions: number of trial for each task.

#### C. Experimental protocol

Subjects were instructed about the tasks that had to be performed before the experiments were conducted.

The subjects sat in a chair holding the handle of the manipulator with their dominant hand. The lower arm was restrained in an arm support such that the axis of rotation of the wrist and the manipulator coincided. The manipulandum controlled the angle of the handle to follow ramp-and-hold trajectories. Through the various excitation signals applied on the manipulandum, the angle of the handle was mechanically changed during the task that included a perturbation. A force transducer in the handle measured the torque applied by the subject. With the wrist in its neutral position (no flexion) the subject was instructed to maintain a constant flexion torque of 1.8 Nm, which approximately corresponds to the 15% of the average maximum voluntary contraction force (MVC) to the manipulandum that an average male subject can apply. The 100% MVC force was then set to this amount and during all of the following force task trials the subject is asked to exert an approximately constant force which corresponds to the 15% of this MVC force. Force tasks with approximately 15% of MVC force (specifically 16%) were proven more effective in revealing high CMC in beta band than those with lower (4%) percentage of MVC force in [40]. This task is equivalent to a 'let go' task, in the sense that task performance is optimal when the subject gives way to the perturbations. The exerted force is fed back to the subject via a computer screen in order to aid the subject in maintaining the right amount of force. All stretches were in flexion direction.

In the beginning of the experiment, 6 repetitions of a force task trial (60 seconds per trial) without perturbation were performed for each subject. This was called base task. In the end, the raw EEG, EOG and EMG for each subject in this force task consisted of 360 seconds.

Afterwards, two multisine perturbations were applied (referred in the report as MS1 and MS2). The reason for applying multisines is the need to examine the effect in coherence from exciting different frequencies. MS1 and MS2 multisines were of different frequency content, as shown in Figure 3. Multisines consist of continuous pulses as position displacements, with an autocorrelation similar to white noise, making them suitable for the estimation of impulse response functions. MS1 is consisted of the frequencies 5,9,13,17,21,25,29 (in Hz) whereas MS2 is consisted of the frequencies 5,7,11,13,17,19,23,29 (in Hz). The peak to peak amplitude of both MS signals is 2 and the length of each of the MS perturbations is 55 seconds. We assume that multisine perturbation do effect corticomuscular coherence. Moreover, we apply two different multisines in order to broaden the spectrum of excited frequencies. In that case we expect to see high coherence in different frequency points in each case of multisine, since the excited frequencies are not all the same. In the same time, by having some common excited frequencies (5, 13, 17 and 29 Hz) we can compare the result in coherence in these common frequencies in each case of multisine and verify the effect of multisine in coherence, in case we find similar high coherence in the common frequencies of the two multisines.

During multisine perturbations' task. the manipulandum moves the wrist according to an unpredictable, smooth, periodic pattern consisting of a sum of sine waves with power at the above mentioned prime frequencies. Each set of force task trials consist of 7 trials (74 seconds per trial). Only in case of one subject (subject 1), 7 additional trials we performed with MS1, in order to acquire more segments of data and examine the effect of the number of segments on the results (we expect that with more segments of the same length the results will be improved). The peak to peak amplitude of the perturbation is 3°. The subject has to give way to the perturbation in order to maintain the required force. Between trials subjects are given as much time to relax as they needed in order to prevent fatigue. The force tasks with multisines resulted in two sets (one for each multisine) of 385 seconds recordings of raw EEG, EOG and EMG for each subject, except in case of subject 1 where the corresponding lengths

 TABLE I

 INFORMATION ON THE FORCE TASKS OF THE EXPERIMENT



Trial of 2 seconds length for both multisine perturbations (MS1-black line, MS2-red line, left plot) and the power spectral density of the multisine perturbations (MS1-black line, MS2-red line, right plot)

were 770 and 385 seconds of recordings having MS1 and MS2 as perturbations respectively.

As the last phase of the experiment, PRBS perturbation (referred in the report as PRBS1) was applied. Pseudo random binary sequences (PRBS) are signals which rapidly switch between two discrete states, in this case positions, at semi-random intervals. This rapid switch of the signal is expressed as stretch velocity, meaning the frequency of the transitions from one value (or state) to the other (see Figure 4). In our case, the manipulandum applied perturbations in the form of rapid but small changes in wrist angle resulting in alternating stretches of the wrist flexors and extensors. The rapid moves between two wrist angles of the manipulandum have unpredictable for the subject intervals. Therefore, the performance of each subject with PRBS perturbation is



Trial of ten cycles for PRBS1 perturbation (left plot) and the power spectral density of the PRBS1 perturbation (right plot)

expected to be much limited comparing with the corresponding in case of base task or multisine perturbations. On the other hand, this kind of perturbation is expected to cause muscles' reflexes that can be seen in EMG, as well as proprioceptive evoked potentials that can be identified in EEG. Therefore, data from PRBS are used in the time domain analysis, whereas in frequency domain analysis they are used only for comparison.

The peak to peak amplitude of PRBS1 is 2, resulting in a 6° peak-to-peak transition of the manipulandum. The length of the perturbation is 62 seconds, whereas the minimum length of a pulse was set to 400 miliseconds. The subject had to give way to the perturbation in order to maintain the required force. For each subject, 10 repetitions of PRBS perturbation were applied. Again only in case of subject 1, 7 additional trials



Schematic plot of the connection between the muscles in the lower arm (FCR : flexor carpi radialis, ECR : extensor carpi radialis) that are contracted due to the perturbation applied on the wrist through the transitions of the manipulandum, and the CNS (central nervous system). CNS consists of the spinal cord (seen in the middle) and the brain (see on top). Afferent signals are generated due to the applied proprioceptive perturbation and transmitted to the spinal cord. The spinal cord sends afferent signals to the brain, as well as efferent signals (motor neural signals) to the muscles which are then contracted. These efferent signals have either spinal origins (fast reflexes), or trans-cortical origins (from the brain). EEG from the brain and EMG from the pre-mentioned contracted muscles are recorded through electrodes attached to the surface of the head and low arm respectively.

were performed with PRBS1 perturbation for the same reason explained above. 620 seconds of raw EEG, EOG and EMG were recorded during this force task for each subject (subject 1 having 1240 seconds of recording). The features of each task are tabulated in Table I. In Figure 5 one can see a schematic representation of the connection of the different structures of the human body which are activates during the experiment. The total experimental time per subject was of 2,5 hours in average. Instruction and electrode placement took about half an hour, while the tasks with pauses took the remaining 2 hours.

#### D.Data preparation

Offline, all data were segmented into trials in two different ways. The first way of segmenting was applied only in the case of the PRBS1 perturbation. The data were segmented according to the timing of the transition of the manipulandum from one state to the other. Since there are two different states (a state where the perturbation has the value of 1 and another one where it has the value of -1), two different events were created. In both events, each segment begins 122 ms prior to the onset of the perturbation (the timing of the transition) and lasts for 400 ms, which is the minimum duration for which the manipulandum stays at one state. This approach serves in looking at the effect of the rapid transition in the EEG response and the EMG reflexes.

The other way of segmenting the trials, depends on the effect that the segment length has in the coherence calculation. Coherence varies depending on the segment length. Segmenting your data into short segments gives you the opportunity to use an adequate amount of segments to compare and therefore CMC can be analyzed in a more reliable way than using longer segments [41]. Therefore the data were segmented with 1 second length.

EMG in all the cases was rectified for the time domain analysis but not rectified for the frequency domain analysis. In the time domain analysis we are interested in the firing times of the signal (as a sign of reflex), so rectification is needed. On the other hand, different studies have pointed out the need to not rectify EMG when studying CMC, since it results in higher values of CMC [42, 43].

For creating EEG segments, artifact removal was performed in order to increase the signal to noise ratio. The noise in EEG is due to EMG and EKG components, as well as due to eye movements and eye-blinking. The formal, were tracked by looking at the EOG recordings and removing any segment that contained increasing activity in EOG. For the rest of the artifacts, Independent Component Analysis (ICA) was applied to the EEG trials. ICA finds temporarily independent components in EEG, without further knowledge about their distributions or dynamics. Therefore, the independent components may even have the same (non-orthogonal) scalp distributions. ICA takes into account higher than second-order dependencies (or independencies) in the component activations. In that way, EKG and eye movements' components were clearly imaged and removed from EEG, leading to a dimension reduction. Moreover, for the line noise of 50 Hz, a band-pass filter (4th order Butterworth, 49 to 51 Hz) was applied in both EEG and EMG trials. The head and arm movement artifacts were removed by applying a high-pass filter (2nd order Butterworth, 5 Hz) in both EEG and EMG respectively. Finally, by examining trial by trial and channel by channel, more trials that appeared to have an abnormal pattern indicating noise were removed. It should be noted here that in the case of S4, there was a leakage of conductive gel on three of the electrodes above the occipital cortex which led to incertitude on the results from this subject.

#### E. Analysis of the data

*Spectral power and coherence calculation.* The fast Fourier transform (FFT) of each of the segments for the two signals being analyzed each time was calculated. The length of the FFT was equal to the length of each segment, consequently, the frequency resolution was 1 Hz (for 1 s segment length). The power spectral density (Gxx) of each signal was calculated as

$$G_{xx} = \frac{1}{N} \sum_{i=1}^{N} \left| X_i(f)^2 \right|$$
(1)

where Xi(f) is the FFT of segment i of a total of N segments of signal x(t). The cross-spectral density (CSD) of the two analyzed signals was calculated according to

$$G_{yx} = \frac{1}{N} \sum_{i=0}^{N} |Y_i(f)X_i^*(f)|$$
(2)

where Xi and Yi are the FFT of segment i of a total of N of signals x(t) and y(t). The star \* represents the complex conjugate.  $G_{xx}$ , as well as  $G_{yx}$  are then averaged over successive data segments, without any overlap with each other. The phase difference of the two signals is given by the angle of the complex function Gyx. Magnitude-squared coherence (here referred to as just coherence) between two signals is defined as

$$\gamma^2 = \frac{G_{yx}^2}{G_{xx}G_{yy}} \tag{3}$$

Coherence is assumed to be significant if the amplitude is higher than the confidence interval Cp given by

$$C_p = 1 - (1 - a)^{1/(n-1)} \tag{4}$$

where  $(1-\alpha)$  represents the level of confidence and n the number of segments over which coherence is being calculated (Halliday et al 1995). In this study  $\alpha$  was set to 0.05 so as to achieve a level of confidence of 95%.

*Time delay.* The time delay between two coherent signals can be calculated by analyzing the phase of their cross-spectral density. Dynamics of the system are neglected with this approach. The approximate time delay is given by the slope of the phase at frequencies where the signals are coherent. For this analysis, a straight line is fitted through such points using the least squares method. The slope of the fitted line is then assumed to be the delay between the two signals.

*Transfer function*. The linear relationship between the output of a system and its input is given by a transfer function:

$$H_{xy} = \frac{G_{yr}}{G_{xr}} \tag{5}$$

where Gyr is the cross-spectral density of disturbance signal r and output signal y. Gxr is the CSD of the disturbance and input signal x. Coherence between the two signals has to be significant for the calculation of the transfer function to be valid.

For all the above procedures, hand written code as well as methods from the open source toolbox, Fieldtrip were used.

*Proprioceptive-evoked potentials analysis (PEP).* Proprioception has been defined as including four kinds of sensations; (1) Sensation of passive movements. (2) Sensation of active movements. (3) Appreciation of position in space and (4) appreciation of force applied [59]. In our case, the felt sensation is of appreciation of force applied due to the unpredictable transitions of the manipulandum that the subjects are handling.

First the power spectral densities of all the EEG and EMG channels were examined. In all the subjects, the power is nearly 0 for frequencies above 80 Hz. Therefore, a low-pass filter (2nd order Butterworth, 80 Hz) was applied to both EEG and EMG signals. The EEG recordings from all segments were aligned with the mechanical perturbation and a baseline correction was applied. Normally, the baseline corresponds to the mean value of the final 100 ms preceding the onset of the perturbation to the wrist. However, the time interval before the timing of each transition couldn't be taken as a baseline, because PRBS1 is a continuous perturbation and therefore a few milliseconds before the timing of the transition, the muscles are also contracted. Therefore, we applied baseline correction by using the data from base task as baseline and removing the average over the segments from base task from the data acquired with PRBS1. PEP are then derived by the following equation:

$$PEP = M_{PRBS_{0\to 0.1}} - mean(M_{base\_task})$$
(6)

Where PEP stands for proprioceptive-evoked potentials,  $M_{acces}$ 

 $M_{PRBS_{0\to0.1}}$  represents average over segments EEG data acquired with PRBS1 perturbation in a time interval of 0 to 0.1 seconds (approximate early cortical activity) and mean( $M_{1,0}$ , )

 $mean(M_{base\_task})$  stands for the mean value of the averaged over segments EEG data derived from base task. The analysis in EMG was based on finding the onset of M2 response. Onset of the M1 segment of the EMG response was defined as the time point when the rectified EMG exceeded three standard deviations from the mean rectified baseline activity calculated from 60 to 40 ms prior to torque onset. Onset of the M1 segment reached a minimum and was followed by a period of increased activity for greater than 10 ms, following the methodology in [1].

*Cross-correlation*. Cross-correlation functions describe the sequential structures of signals. Cross-correlation is a measure to analyze relationships between signals, often a system's input and output. The cross-correlation function between two signals x(t) and y(t) is defined by

$$\varphi_{xy}(\tau) = \mathbf{E}[x(t-\tau)y(t)] \tag{7}$$

where  $\tau$  is the lag of signal x(t) in relation to signal y(t).

#### F. Surface current source density (Laplacian derivation).

CSD surface analysis has been developed independently as reviewed in detail in [46]. Skull current density estimates are obtained by means of surface Laplacian algorithms. Laplacian derivation serves as high-pass spatial filter that accentuates localized activity and reduces more diffuse activity. The Laplacian algorithms have a meaning only in cases of a dense electrode montage, as in our case. The value of the Laplacian at each electrode location is calculated by combining the value at that location and the values of a set of surroundings electrodes. The distances to the set of surroundings electrodes determine the spatial filtering characteristics of the Laplacian. As distance decreases, the Laplacian becomes more sensitive to potentials with higher spatial frequencies and less sensitive with lower spatial frequencies.

In the current study, to calculate the Laplacian derivations we used a finite difference method, which approximates the second derivative by subtracting the mean activity at surrounding electrodes from the channel of interest. The Laplacian was computed according to the formula

$$V_i^{LAP} = V_i^{CAR} - \sum_{j \in Si} g_{ij} V_j^{CAR}$$
(8)

where

$$g_{ij} = 1/d_{ij} / \sum_{j \in Si} 1/d_{ij}$$
(9)

Si is the set of four electrodes surrounding the  $i^{th}$  electrode,

and  $d_{ij}$  is the distance between electrodes i and j (where j is a member of the four surrounding electrodes). The four surrounding electrodes were chosen based on the so-called large Laplacian difference, which in [25] was set to 6 cm distance from the electrode of interest to the rest of the surrounding electrodes' set. In that research, large Laplacian derivative gave the best results in CMC comparing to CAR and the small Laplacian derivative (set to 3 cm to set of surrounding electrodes). In our case, we defined the set of surrounding electrodes by looking on the electrode of interest. Laplacian CSD is considered the standard derivation for this study.

#### G.Intracranial current source density methods

Intracranial current source density methods are procedures to solve the so-called inverse EEG problem, using a gain matrix derived from the solution of the forward EEG problem. Forward EEG problem correlates the EEG recordings with some sources modeled as dipoles located in the brain which is modeled as a volume conductor. The forward model is represented by the following equation :

$$M = L(r)D(r) + n \tag{10}$$

where r the location of the dipole and time component, M is a matrix Nx1 scalp readings, with N number of EEG channels (in our case being 64), L is the gain matrix (Nxmdimension, m being the number of the underlying dipoles in the brain), D is the source matrix with source moment (mx1) and n representing the noise. Under this notation and by implying zero contribution of noise (taken for granted in the rest of the study), the inverse problem then consists of finding an estimate D of the dipole magnitude matrix given M and using L, which can be expressed in the following equation :

$$D(r) = B(r)M =$$
  
= B(r)L(r)D(r) = R(r)D(r) (11)

Where B is the inverse matrix, so-called spatial filter, and R being as close as possible to the unitary matrix I. The source generators of the cerebral evoked potentials were modeled using spatio-temporal dipole source analysis, based the Matlab software toolbox for EEG analysis, Fieldtrip.

*Head model.* The head model can be either an overapproximation of the actual individual head (a spherical model), or can be derived from anatomical images (Magnetic Resonance Imaging, MRI in most cases) and require computationally intensive numerical techniques. There is no accurate proof that the second case offers better results than the first one, even if an indication for this contingence has been reported by many researchers. Therefore, in our study the effects of volume conduction of the field potentials to the surface of the scalp were modeled using two different head models, a spherical one and a realistically shaped one.

The spherical model was a four-shell spherical head model (head radius 85 mm; scalp thickness 6 mm, conductivity 0.33 mho/m; bone thickness 7 mm, conductivity 0.0042 mho/m; CSF thickness 1 mm, conductivity 1 mho/m; brain conductivity 0.33 mho/m). Equivalent current dipoles were quantified based on their location within the spherical head model, orientation with respect to a vertical and transverse axis and a magnitude reflecting the equivalent dipole moment. Electrodes' position should then be aligned to the model. The source grid was defined inside the brain with a spatial resolution of 1cm. The origin of the Cartesian coordinate system within the head model corresponds to the center of the head with an x-axis (medial/lateral) pointing to the right through T4, a y-axis (anterior/posterior) through FPz and a zaxis (dorsal/ventral) upward through Cz. Orientation of the dipole vector is reported as theta (q) and phi (f), corresponding to polar angles with respect to the vertical (z) and medial/lateral (x) axis, respectively (for further details, see [1]).

On the other hand, the realistically shaped head model was derived from a template MRI from Montreal Neurological Institute (MNI). First the MRI is segmented so as to define the anatomy of white, gray matter and cerebrospinal fluid (CSF) in the brain. Then the skull and the skin layers are also defined and distinguished as different tissues, resulting in a model of three different tissues (brain, skull, skin). The conductivity values assigned on these three layers were 1 mho/m, 0.0125 mho/m and 0.33 mho/m for brain, skull and skin respectively. On the other hand, the geometry of the head model is totally

dependent on the dimension of the MRI. The head model was based on Boundary Element Method (BEM) to define the triangulated surface meshes of each tissue of the volume conduction model [47]. For further information on these two models, see Appendix A.

Dynamically Imaging of Coherent Sources (DICS): DICS is an intracranial source density method that estimates functional connectivity between cortical areas and a reference neural source or electrode (EEG or EMG). In our case, we used DICS to find the cortical sources that are coherent with the EMG activity recorded from flexor carpi radialis muscle in EMGflex channel. It actually uses a spatial filter to localize coherent brain regions and provides the time courses of their activity. In every brain region, a number of dipoles are placed in pre-defined locations of the source grid.

The spatial filter in DICS (B form Eq.11), is created by a linear transformation which satisfies the following formula:

$$\min[\wp \{ \|BM_f\|^2 \} + a \|B\|^2 ], \text{ subject to}$$
$$BL(r) = I$$
(12)

where B the spatial filter,  $M_f$  a matrix that contains the Fourier transformed EEG data,  $\mathcal{O}^{\{\}}$  denotes the expectation value, a is a regularization parameter and L(r) contains the solution of the forward problem for two orthogonal tangential unit dipoles at r. By applying the above formulation to the measured data, the activity is passed in a specific frequency band of the sources at position r with unit gain, while suppressing contributions from all other sources. The constraint ensures that the desired signal is passed with unit gain. By minimizing the corresponding Lagrange function, the frequency-dependent solution can be derived in analogy with [48].

$$B(r, f) =$$

$$= (L^{T}(r)G_{r_{xy}}(f)^{-1}L(r))^{-1}L^{T}(r)G_{r_{xy}}(f)^{-1}$$
(13)

where  $G_{r_{xy}} = G_{xy} + aI_{and} G_{yx}$  the cross spectral density matrix between the EEG channels of interest and EMGflex channel at frequency f and superscript T indicates the matrix transpose. The last two terms in Eq. 14 represent a weighting of L(r), with the inverse of the cross spectral density matrix. The bracket contains a scaling of the coefficients, which emerges from the constraint in Eq. 13. The power at the dipole location is estimated by

$$P(r,f) = B(r,f)G_{xy}(f)B^{*^{T}}(r,f)$$
(14)

The corresponding equation for the cross spectral density between each source and EMGflex channel can be computed according to

$$g(r,f) = B(r,f)G_{xy}(f)$$
(15)

From Eq. 14 and 15, it is evident that the power estimate can thus be computed efficiently from the solution of the forward problem and the cross spectral density matrix. If the singular values of  $g \lambda_1 >> \lambda_2$ , the cross spectrum can be attributed to sources with fixed orientations, determined by the singular vectors corresponding to  $\lambda_1$ . We can then reduce the matrix in Eq.15 to scalars by estimating the cross spectral density along the dominant direction, which leads to the expression

$$g_s(r,f) = \lambda_1 \{g(r,f)\}$$
(16)

Where  $\lambda_1$  indicates the larger singular value of the expression in braces. Analogously, the power in the dominant direction is

$$P_s(r,f) = \lambda_1 \{ P(r,f) \}$$
<sup>(17)</sup>

Then a new corticomuscular coherence can be then calculated from equations 16 and 17, which is

$$\gamma^{2}(r,f) = \frac{|g_{s}(r,f)|^{2}}{P_{s}(r,f)G_{yy}(f)}$$
(18)

where,  $G_{yy}(f)$  is the auto-spectral density of the EMGflex channel at frequency f. A more detailed description of the method can be found in [44]. EEG and EMG data used in this analysis were only the ones derived from force tasks with multisine perturbations.

Dipole fitting. Dipole fitting is an intracranial CSD approach, through which the whole dipole grid is scanned so as a

location to be found in which a dipole-source can be fitted, the excitation of which explains in the most precise way the recorded EEG topography in the defined time interval. In contrast to DICS described above, a number of dipoles should be assigned in advance. In our study, the number of dipoles that model the early cortical activity of the EEG data was set to three (three-dipole model), based on the results from a relative study in [1].

The procedure is initiated by first finding a starting point for the non-linear dipole fitting. The starting location can be found either by making an initial guess on the location(s) of the dipole (s) (saving like this time and reducing data load), or by performing a global grid search, during which a scan is performed on every dipole-location of the sources grid. Assuming that the estimated source moment is expressed as

$$\hat{D}(r) = \lambda_1 \{ L(r) \} M \tag{19}$$

where all the variables and symbols are explained above. The modeled then EEG topography is derived from

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$$U = L(r) D(r) =$$
  
=  $L(r)\lambda_1 \{L(r)\}M$  (20)

The starting dipole location would then be the one in which the error between recorded and modeled EEG topography is minimized, as expressed in the following equation

$$r_{dip,start}:\min(\left\|M-U\right\|)$$
(21)

After the starting point has been set, non-linear fitting is initiated. During non-linear dipole fitting, dipole solutions are generated by iteratively changing both the location and orientation of the assigned dipoles within the head model. The modeled EEG topography is calculated in every location that a dipole is fitted using again the equations 20 and 21. The best fit is achieved by applying ordinary goodness-of-fit measures and specifically the relative residual variance function (RV) on the EEG surface signals over the specified time range, which is expressed as

$$r_{dip,fitted} : \min(rv) = \min(\frac{\sum_{i=1}^{N} (M - U)^{2}}{\sum_{i=1}^{N} M^{2}})$$
(23)

|                   | EEG CHANNELS OF INTEREST         |                       |
|-------------------|----------------------------------|-----------------------|
| Electrode         | Region of the cortex             | Derivations           |
| FC5               | Premotor cortex                  | Laplacian             |
| FC3               | Premotor cortex                  | Laplacian             |
| FC1               | Premotor cortex                  | Laplacian / DICS      |
| FCz               | Primary motor cortex             | Laplacian             |
| <i>C5</i>         | Primary somatosensory cortex     | Laplacian             |
| C3                | Primary motor cortex             | Laplacian / DICS      |
| C1                | Primary motor cortex             | Laplacian             |
| $C_{\mathcal{Z}}$ | Primary motor cortex             | Laplacian / DICS      |
| СР3               | Primary somatosensory cortex     | Laplacian             |
| CP1               | Primary somatosensory cortex     | Laplacian / DICS      |
| CPz               | Primary somatosensory cortex     | Laplacian             |
| Р3                | Somatosensory association cortex | Laplacian / DICS      |
| P1                | Somatosensory association cortex | Laplacian / DICS / DF |
| Pz                | Somatosensory association cortex | Laplacian             |

TABLE II FEG CHANNELS OF INTERES

List of the EEG channels of interest. Region of the cortex: above which region each electrode lies. Derivation: spatial filter used on each electrode. DF = Dipole fitting. DICS: Dynamically Imaging Coherent Sources

A more detailed description of the method can be found in [45]. EEG and EMG data used in this analysis were only the ones derived from force tasks with PRBS perturbation.

The flow chart of the work flow of this study can be seen in Appendix B.

#### III. RESULTS

Among the different EEG channels, we present the results only from those above the premotor, the primary motor, the primary somatosensory, as well as the somatosensory association cortex of the left hemisphere, which is defined as the contralateral one in all the five right-handed subjects. The results in these channels were better than in the rest, as expected.

*EEG - perturbation coherence.* Coherence between EEG signals acquired from each of the force tasks with MS1, MS2 and PRBS1 perturbations and their corresponding perturbation applied to the wrist was computed.

In case of multisine perturbations (MS1 and MS2), two out of five subjects (S4 and S5) didn't reveal coherence above the level of significance in almost all the EEG bands. In the rest of the subjects, coherence was above the level of significance in all the excited frequencies above 13 Hz in almost all the EEG channels of Table II. In frequencies below 13 Hz coherence was much lower and barely above the level of significance. Among the EEG channels, the ones above the pre-motor cortex showed the worst results. On the other hand, the channels above the primary motor cortex showed high coherence in the low frequencies of the beta band, especially at 17 Hz, where in channel C3 the values varied from 0.17 to 0.27 (in S3). Channels above the primary somatosensory cortex and above the somatosensory association cortex showed good results in the higher frequencies, especially at 29 Hz. In channels P1 and P3 above the somatosensory association cortex coherence varied from 0.17 to 0.39 and from 0.1 to 0.37 respectively, whereas in channel CP3 of the primary sensory cortex coherence varied from 0.06 to 0.31. In Figure 6, the average coherence results over the three subjects showing good results (S1,S2,S3) with MS1 perturbation over all subjects in all the EEG channels are plotted.

However, in case of PRBS1 perturbation, significant coherence is found in only a few frequency points as expected, with a much lower value than in the case of MS1 or MS2. Only in two subjects (S2 and S3) coherence was above the level of significance in some channels but still it doesn't exceed the value of 0.05. The channel with the most coherent frequency point in these subjects is channel C3. The effectiveness of the multisine perturbations in contrast to PRBS one in revealing significant perturbation to EEG coherence is imaged in Figure 7.

*EMG - perturbation coherence.* Coherence between each perturbation applied to the wrist (MS1, MS2 and PRBS1) and the EMG channel, EMGflex, was also computed. Once more, when using multisine as perturbation signal, coherence is above the level of significance in almost all the excited frequencies, a fact seen this time in all the subjects. In Figure 8 one can see the average over all subjects' coherences between EMGflex channel and the MS1. On the other hand, only a few frequencies show coherence above significance in the case of PRBS1 perturbation, having very low values. In contrast to the case of EEG to PRBS1 perturbation coherence, the results in this case are more accordant among the five subjects, in each of whom some significant but very low coherences were calculated. A comparison between the results with multisines as perturbation

(MS1 and MS2) and with PRBS1 perturbation can be seen in Figure 9.



Figure 6 Average coherence between perturbation (MS1) and EEG in the channels of the sensory-motor cortex (the red dotted line indicates the level of significance)



Figure 7 Coherence between MS1 (black stars), MS2 (magenta stars) and PRBS1 (green line) perturbations and the EEG channel C3 of the primary motor cortex (the red dotted line indicates the level of significance)



Figure 8 Average coherence between perturbation (MS1) and EMGflex channel (the red dotted line indicates the level of significance)



Figure 9 Coherence between MS1 (black stars), MS2 (magenta stars) and PRBS1 (green line) perturbations and the EMG channel EMGflex (the red dotted line indicates the level of significance)



Average corticomuscular coherence in MS1 in the channels above the sensory-motor cortex (the red dotted line indicates the level of significance)



CMC between channel C3 of EEG and EMGflex from base task (blue line), force task with MS1 (black line), with MS2 (magenta line) and with PRBS1 (green line) perturbations (the red dotted line indicates the level of significance)

each channel of EEG and EMGflex channel during base task, as well as

during force tasks with MS1, MS2 and PRBS1 perturbations was calculated too. In case of base task, the average coherence over all subjects is below significance for all the EEG channels. In two out of five subjects (S2 and S5) corticomuscular coherence in the channels above the premotor and primary motor cortex (especially in the FC1,FC3,C3 and C1 channels) was above the level of confidence in frequencies of 14, 26,27, 30, as well as 40 and 44 of the beta and gamma band respectively.

In case of the force task with MS1 perturbation, three out of five subjects showed good results, with the average results shown in Figure 10. Once more S4 and S5 didn't reveal significant CMC in almost all the frequencies of the different EEG bands, a result expected from the analysis of the MS1 and MS2 to EEG coherence. Channels above all the primary motor, the primary somatosensory and the somatosensory association cortex showed very good results with the best found in C1, C3, CP1, CPz and P3 in average. Among the different frequencies excited, coherence was higher at 17 Hz, 25 Hz, and 29Hz, especially in channel P1 in S3 at 29 Hz coherence reached the value of 0.24. In two of the three best subjects (S1 and S2) and in almost all the fourteen channels, CMC was significant and also high also at 42 Hz, which is the first harmonic of 21 Hz. In S1, we find low but significant CMC also at 34 Hz (first harmonic of 17 Hz). Moreover, in S2 CMC was significant and quite high in 51 Hz, a frequency point close to the first harmonic of 25 Hz. Finally, significant coherence was found also in frequencies of the gamma band that are not harmonics of any frequency included in the perturbation spectrum, like in 38 Hz in S2, in 46 Hz for S3 and S5 and 54 for S5.

In case of the force task with MS2 perturbation, three out of five subjects showed good results (S4 and S5 didn't reveal significant CMC again). In the rest of the subjects CMC was above the level of significance in most of the excited frequencies of the beta band (17, 19, 23 and 29 Hz). The channels with the best results are the same as in case of MS1, including also Pz. Once more, coherence was higher at 17 Hz and 29Hz, especially in the P channels were in case of S3 the average coherence in these three channels at 29 Hz is 0.28. One difference with MS1 is that having one more perturbed frequency of the alpha band (at 11 Hz), coherence was found also at that frequency point but only in the channels above the association somatosensory cortex. CMC was found in frequencies that are not excited too. Specifically, CMC was above the level in most of channels in the first harmonic of 23 Hz (at 46 Hz), as well as at 38 Hz, a frequency point which does not consist a harmonic.

Finally, in case of PRBS1 perturbation CMC is almost in every point below the level of confidence in all the subjects. This time, only S3 showed some coherence values above the level of confidence, especially in the frequencies of mu band (8 Hz to 13 Hz), but with maximum value of only 0.06 at 11 Hz in channel CPz. A comparison of the results in CMC for all the force tasks with different perturbations can be seen in Figure 11.

Transfer function calculations were made only for the data acquired from force tasks with MS1 and MS2 perturbations, since these were the only cases in which we found significant coherence between the signals of the system. In the frequencies that coherence is above significance, the transfer function can be reasonably evaluated. Results from 5 Hz are not plotted since the coherence was below level of significance in almost all the subjects.

*Perturbation – EEG transfer function.* The transfer functions between EEG channel C3 and MS1, as well as MS2 perturbations were computed (Figure 12). The gain is fluctuated around 1 and 0.5 for MS1 and MS2 cases respectively. Unfortunately, the pattern of the phase of the coherence didn't allow us to fit a line and estimate the mean delay between perturbation and EEG.

*Perturbation – EMG transfer function.* The transfer function between EMGflex and its corresponding perturbation applied to the wrist was computed (Figure 12). The results of transfer function in that case are more reliable since the coherence of perturbation to EMG is very high. The gain in that case is very high, and it is increasing when moving to higher frequencies, in all the subjects in both cases of multisines. The approximate slope of the transfer function magnitude for MS1 case varies between 50 and 133, implying that the sensed information comes from stretch rate proprioceptors. No time delay estimation could be derived from the results in phase in case of MS1, whereas in case of MS2 there is an obvious decrease in phase with frequency. However, no time delay between the two signals was estimated.



Figure 12. Averaged transfer function plots between all signals of the force task with MS1 perturbation (black lines) and MS2 perturbation (magenta lines). The red line indicates the level of significance.

*EEG – EMG transfer function.* The transfer function between C3 EEG channel (having in average the best coherence results)

and EMGflex was also calculated for the case of the two multisine perturbations (Figure 12). CMC is above the level of significance almost at all frequencies above 9 Hz. There is an apparent increase in the gain with frequency in both cases, starting from 3 at 11 Hz and ending up in 11.1 at 29 Hz in case of MS2. Phase information for the transfer function could not be derived from the phase patterns.

Source localization of corticomuscular coherence using spherical head model. The resolution of the source grid in the model was set to 1 cm. Therefore, one dipole corresponds to one voxel of 1cm<sup>3</sup>. The dipole grid consisted of 981 dipoles. Coherence between each dipole in the grid and EMGflex channel was calculated at the four excited frequencies in the beta band (17 Hz, 21 Hz, 25 Hz and 29 Hz), as well as at two harmonics, 34 Hz (first harmonic of 17 Hz) and 42 Hz (first harmonic of 21 Hz), since high CMC was found in these frequencies too in part 3.1.

By using every time the cross-spectral density matrix between each of the EEG channels and EMGflex channel, we are looking on the dipole in the model that shows the highest coherence with EMG recording. DICS method was used in this analysis.

Even if the value of the highest value of coherence varied over subjects, the location of the dipoles with the highest coherences was the same in all five subjects and for all different frequencies. The coordinates of this dipole are: x=-6, y=-1, z=2. It lies below channel CPz in the ipsilateral primary somatosensory cortex, very close to the central sulcus that separates the primary motor cortex with the primary somatosensory cortex. In Figure 13 the average over subjects coherence between the afore-mentioned dipole and EMGflex is plotted, in six different cases of EEG channels. Coherence through DICS is compared with CMC calculated by using only Laplacian derivation. CMC with Laplacian derivation is slightly higher than coherence acquired with intracranial CSD, except in channel P3, in which intracranial CSD results in higher coherence at 29 Hz.

Source localization of corticomuscular coherence with realistically shaped head model. The resolution of the source grid in this model was also set to 1 cm. The dipole grid consists of 682334 dipoles. Coherence between each dipole in the grid and EMGflex channel was calculated at the same excited frequencies as in the case of the spherical model. The highest values of CMC were exactly the same in both models, as expected due to the common values of conductivity set to both models. The location though of the dipoles with the highest CMC differs. That was also expected due to the different geometry of the models. In Figure 14, the grid of coherence with DICS at 29 Hz superimposed on the anatomical MRI is plotted in three different ways; in an

'orthogonal cut', slice by slice going from the surface of the brain to the inner planes and finally by projecting onto a surface of the brain. Looking on the projection of CMC onto the surface of the brain, we identify two main regions with coherence around 0.16, which is above the level of confidence. One region is approximately the supplementary motor area of the sensorimotor cerebral cortex which lies on the medial face of the hemisphere, just in front of primary motor cortex. Another region showing high coherence in Figure 14 is localized deep in the brain, at the temporal cortex in the frontal lobe.

*EMG responses to rapid angular displacements of the wrist.* The application of rapid angular extensor displacements on the wrist via PRBS1 perturbation, generated distinct M1 and M2 responses in FCR in four out of the five subjects. Only S2 didn't show clear early EMG activity. An example of the average rectified EMG response evoked across tasks for both FCR and EDC is shown for a single subject (S1) in Figure 15.

Following the procedure of identifying M2 timing, the onset of LLSR could be identified. However, a clear separation between the activity labeled M1 and M2 and also between M2 and the onset of the voluntary activity was observed only in two of five subjects, and specifically in subject 1 (see Appendix C) and subject 4. In other subjects, the separation between M2 and voluntary activity was less pronounced (S5) or was only represented by a small inflection (S3). The mean onset latencies across subjects for the M1 segment were  $23\pm5$ ms. The corresponding onset latencies for the M2 segment were  $68\pm1$  ms.

*Evoked potentials to rapid angular displacements of the wrist.* The topography of the grand average EEGs for all subjects over the collection epoch from 25 ms before to 150 ms after the onset of the PRBS perturbation is shown in Figure 16. The high positive amplitude in the occipital cortex is probably due to eye-movement artifacts, which were not removed during preprocessing phase.

The early components of the evoked potentials were not characterized by the same small amplitudes at the corresponding channels of each subject. However, peaks, that could be defined as PEPs were found in the responses of all subjects. Here we plot results from subject 1 (Figure 17), who showed more plausible PEP than the rest and also because this subject showed the clearest EMG involuntary responses (clear M1, M2). In order to be able to distinguish the peaks that can be defined as ERPs, baseline correction was performed as described in part 2.5.4. (see Appendix C) The early cortical evoked activity is defined in the interval of 45 ms to



Average corticomuscular coherence (CMC) with Laplacian derivation (black stars) and DICS (blue stars) in six of the channels above the sensory-motor cortex.

75 ms after the onset of the perturbation [20]. However noticing an earlier cortical response starting from 15 ms, we initially consider as early cortical activity even the responses found from 15 ms to 45 ms.

A small simultaneous central and post-central positive amplitude can be seen at FC3 with an onset of 14 ms (that can be termed the P14) and a peak amplitude of 0.5  $\mu$ V and at C3, C5 and at CP3 with an onset of 20 ms (that can be termed the P20), as well as a pre-central positive amplitude at P3, P1 and Pz with an average peak amplitude of 0.5  $\mu$ V too.

In the time interval from 45 ms to 75 ms, five peaks are identifying in three channel of the pre-motor and primary motor cortex, a positive amplitude at FC5 and C5 (that can be termed P50) with an average amplitude peak of 0.31  $\mu$ V and an onset at 45 ms, together with a negative peak at channels FC1,FCz, C1 and Cz (that can be termed N50) with an average amplitude peak of 0.46  $\mu$ V and an onset at 44 ms, a positive peak at channel C3 with an onset at 55 ms (that can be termed P60) and two negative amplitudes (termed N60) at channels FCz and Cz with an average amplitude peak of 0.66  $\mu$ V respectively. Finally, a positive central late-response if found

at channels CPz and Pz with an onset at 60 ms (that can be termed the P70) with an average amplitude peak of 0.6  $\mu$ V and a central and post-central positive amplitude at channels Cz, C1, FCz and FC1 with an onset at 70 ms (that can be termed the P80) with an average amplitude peak of 1.2  $\mu$ V.

Source localization of proprioceptive-evoked potentials using the spherical model. The resolution of the grid was set to 1 cm. A three-dipole solution was required to sufficiently model the PEPs over the time interval from the onset of the P20 to the peak of the N75 component. Dipole source analysis of the grand average potentials over the time interval of 20–75 ms yielded solutions with average RV's of 7.0%, 3.5%, 2.6%, 3% and 3.7% for subjects S1,S2,S3,S4 and S5 repsectively. This result denotes that approximately 93%, 96.5%, 97.4%, 97% and 96.43% of the whole recorded EEG is explained by this three dipoles model in the five subjects respectively. Except subject1, in all other subjects two dipoles are located below the contralateral motor cortex, whereas one is always located below the ipsilateral motor cortex (see Appendix D). Two of the three dipoles in case of S1





#### Figure 14.

Top left plot : orthogonal plot of the projection of CMC on MRI, where i,j,k axis are in millimeters and denote the size in voxels of the brain. The yellow marked area denotes the regions where we found coherence above 0.1. Finally, the blue cross denotes the location of the dipole with the highest value of coherence.

Top right plot : projected CMC on transverse slices of MRI, moving from the surface of the brain (top right image) to the deepest region of the brain (bottom left image). The yellow marked area denotes again the regions where we found coherence above 0.1.

Bottom plot : projection of CMC on brain surface.

The projected coherence between brain sources and EMGflex channel was calculated at 29 Hz from subject's 3 data. The bars on the sides define the value of CMC.



time (msec) Figure 15.

Electromyograph (EMG) responses in flexor carpi radialis (FCR) and extensor digitorum communis (EDC) over the first 200 ms following torque onset in a single subject (S1). The plot on the left demonstrates the segmentation of the FCR response into a shortlatency (M1), long-latency (M2) and later voluntary (Vol) response.



Figure 16.

Grand average scalp-surface topography of the average EEG potentials elicited by imposed wrist extension displacements over the time interval of -25 to 150 ms after the onset of the transition in PRBS1.



Figure 16.

Early proprioceptive-evoked response in four EEG channels above the senori-motor cortex (time interval from 0 to 130 ms after the onset of PRBS1 perturbation) According to the baseline removal method, we identified some PEP on this early activity. Here these PEP are defined at the timing of their peak 1.

were localized very close to each other (dipole1 and dipole3) in the contralateral primary motor cortex in the central sulcus. The topographic plot of the EEG topography from the original recorded data and the results from the model are plotted in Figure 18. The difference between the two topographies is also plotted, demonstrated as the EEG<sub>recorded</sub> to EEG<sub>modelled</sub> ratio. The only difference noticed is high EEG amplitude in the ispilateral side of the head in EEG<sub>recorded</sub>, with the activity in that part of the head being eliminated with the model. In Figure 19, the moments of the three dipoles are plotted. Due to a peak in dipole3's activation around 60 ms, it can be assumed that this dipole explains P60 in channel C3 of S1. Finally, we calculated the correlation between each of the EEG channels and EMG in both cases (EEG<sub>recorded</sub> and EEG<sub>modeled</sub>). The result of cross-correlation are plotted in Figure 20. The correlation values are similar for the two cases, which strengthens the fidelity of the model towards the reliable representation of the recorded EEG.

Source localization of proprioceptive-evoked potentials using the realistically shaped head model. The resolution of the grid was also set to 1 cm We used the realistically shaped model to perform dipole fitting on the data from S1, being the subject with the best results in time domain analysis. Even if we initiated the procedure of dipole fitting with three dipoles, the dipoles finally overlapped with each other. Therefore, only one dipole is enough to explain the grand average potentials over the time interval of 20–75 ms of S1. However, this time RV 38.6%, meaning that only 61.4% of the whole recorded early evoked activity is explained by this one dipole.

Furthermore, we applied dipole fitting on each of PEP identified in S1, this time using only one dipole to model this activity. The time interval this time was set to 5ms preceding the timing of PEP's peak and 5ms following it. Dipole fitting on P14, P20, P30, P/N50, P60, P70 and P80 was performed. However, only in case of the P/N50 PEP, a dipole could be fitted. The resulted RV was low enough, Approximately, 89% of the EEG activity between 45ms to 55ms is explained by this dipole.

The location of the two dipoles that could explain the whole early cortical activity and activity around 50ms respectively is approximately the same. In Figure 21 we present the location of the dipole derived by dipole fitting on P/N50. It lies approximately in the basal ganglia.



Figure 17.

Topographic plots of recorded EEG (top left plot) and modeled EEG from the dipole fitting procedure (top right plot) The latter topography is the result from the excitation of the three dipoles in the spherical model that model the early cortical activity in EEG data from subject 1. The bars on the side define the level of EEG responses. The ratio of recorded to modeled EEG is also plotted (bottom plot) where this time the side bar defines the level of difference in EEG amplitude in different areas of the electrode montage on the surface of the head. The time interval of all the afore-mentioned topographies is from 15 ms to 100 ms after the onset of PRBS1 perturbation.



Figure 18. The time course of the moments modeled by the three dipoles in the spherical head model (green – dipole1, blue – dipole2 and red – dipole3) in a time interval of 0 to 100 ms (early cortical activity).



Figure 19. Normalized cross-correlation plot of the recorded EEG data (black line) and the modeled EEG from the three dipoles mode with the spherical model (blue line) both acquired from C3 channel above the primary motor cortex



Figure 20

Orthogonal plot of the MRI from which the realistically shaped head model was acquired in order to show (blue cross) the location of the dipole that explains the observed peak around 50 ms after the onset of PRBS1 perturbation in some EEG channels above the sensorimotor cortex. Again here i,j,k axis are in millimeters and denote the size in voxels of the brain.

 TABLE III

 SUMMARY OF EXPERIMENT'S RESULTS

|           |     |                     | -              |                                |                                    |                 |     |
|-----------|-----|---------------------|----------------|--------------------------------|------------------------------------|-----------------|-----|
| Subjects  | NS  | γ <i>EEG</i> - pert | γEMG -<br>pert | γ <i>EEG</i> –<br>EMG@5to13 Hz | γ <i>EEG</i> −<br>EMG@beta<br>band | EMG<br>reflexes | PEP |
| S1        | +   | +                   | +              | +/-                            | +/-                                | +               | +   |
| <i>S2</i> | +/- | +                   | +              | +/-                            | +                                  | -               | +/- |
| <i>S3</i> | +   | +                   | +              | +/-                            | +                                  | +/-             | +/- |
| <i>S4</i> | +   | -                   | +              | -                              | -                                  | +               | +   |
| \$5       | +/- | -                   | +              | -                              | -                                  | +/-             | +   |
|           |     |                     |                |                                |                                    |                 |     |

NS: the number of good EEG segments remained after pre-processing.  $\gamma$ EEG-pert:coherence between perturbation EEG,  $\gamma$ EMG-pert:coherence between perturbation EMG  $\gamma$ EEG-EMG@5to13 Hz: corticomuscular coherence at low frequencies,  $\gamma$ EEG-EMG@beta band: corticomuscular coherence from 18to 30 Hz, EMG reflexes : clear separation between SLSR and LLSR in EMG, PEP:proprioceptive-evoked potentials found in early activity of EEG, + = good, present. +/- = fair, present but not consistent. - = bad, not present.

#### IV. DISCUSSION

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A qualitative summary of the results for this study is presented in Table III. The relationships between the displayed data, as well as the fidelity of intracranial CSD on revealing the sources in the brain active when performing force tasks with wrist perturbation are analyzed in this section.

Perturbation - EEG connection. Coherence between perturbation signals and EEG was found in three out of five subjects and only in the case when we applied multisine as perturbation. In case of PRBS1 perturbation coherence was below the level of confidence in almost all the frequencies of mu, beta and gamma band. Force tasks show a phase lead of around 90°. This suggest that the EEG activation is mediated by group Ia afferents from muscle spindles of the stretched muscle, which keeps track of how fast a muscle stretch changes (the velocity of the stretch) and not by II afferent group which firing rate is directly related to the change muscle's length. The latter conclusion is also strengthened by the fact that in case of PRBS, when the length of the muscle is instantaneously changed, no coherence was found. It has been therefore shown that beta band signals can be generated also from afferent contribution. Multisine perturbation is sensed by the muscle spindles and sent via afferent fibers into the somatosensory cortex. This conclusion matches with the results in [17], where they state that receptors on the hand do not contribute as much on cortical evoked activity as muscle spindles.

The fact that only 3 of the 5 subjects showed significant coherence cannot be yet explained. EEG recordings from subjects S4 and S5 may have been flawed, either by incorrect electrode placement (S4, see Section 2.4), or by excessive blinking and other body movements (S5).

*Perturbation – EMG connection.* Force tasks show also here phase lead, that is different for MS1 and MS2  $(24^{\circ} \text{ and } 90^{\circ} \text{ respectively})$ . This suggests that the spinal reflex is dominated by velocity proprioceptors in such tasks. The latter conclusion is accordant with the findings of Ruiz et al. [41], where they

compared position with force tasks in a study of finger perturbation and they concluded that for tasks where a given force has to be applied, stretch velocity proprioceptors provide most of the feedback, probably as a way to maintain stability. Similar results have been found in ankle experiments [49].

*Corticomuscular coherence.* When using multisine as perturbation, CMC was above the level of significance, especially at perturbed frequencies of the beta band (above 11Hz), in subjects S1,S2 and S3. Could this be an indication of afferent signals' contribute to the muscle activation? Kilner *et al.* [2] reported weak corticomuscular coherence in a deafferented subject and suggested that the sensory afferents would normally contribute to the corticomuscular coherence. In line with this, block of cutaneous feedback from the hand also leads to reduced corticomuscular coherence [50], implying a contribution from afferent signals to CMC. However, we cannot make any conclusion on the contribution of afferent signals to CMC through our study, since corticomuscular synchronization is more likely caused by the common input to both structures, which is the perturbation.

CMC in S2 was above the level of significance in base task, in frequencies of the beta as well as the gamma band The fact that CMC was very low during base task in the same frequencies in which it was high during multisine perturbation strengthens the assumption of a non-direct corticomuscular connection.

The lack of CMC in four out of five subjects can be probably justified by assuming bad trials in the case of base task. Another reason can be the way the limit of 100% MVC was chosen. Since the 100% MVC value was constant for all the subjects, been taken as an approximation of the maximum force than an average subject can apply, there might have been a misbalance on the force applied by each subject on the manipulandum during base task. CMC has been found during base task of wrist perturbation on the non-affected side of patients after subcortical stroke [51] reaching values of 0.2. In that study, CMC above level of significance was found in frequencies of beta and gamma band. Previous studies have also shown disparate levels of coherence across subjects. In the study of Conway et al [52], the level of corticomuscular coherence was fluctuated from 0.02 to 0.14, and the frequencies at which they appeared ranged from 15 Hz to 25 Hz. In Ruiz et al. study [41], CMC was found in only three out of five subjects with good EEG recordings. In Omlor et al study [53] the average coherence across all subjects had a maximum value of 0.03, but with six of the eight subjects showing an average of maximum coherence of 0.007, which is below the significance level of 0.01. This suggests that out of the 8 subjects, up to 6 could have shown no significant corticomuscular coherence around 20 Hz.

CMC was above the level of significance also in the gamma band in base task, as well as in force tasks with multisines. Since our force tasks were visuomotor tasks with proprioceptive input, we expected to find coherence in frequencies of this band too. However, the points with high CMC are still less than in case of [53] where they did found high CMC in this band.. The difference of these studies with ours is that they had both dynamic force and position tasks in contrast to ours where we had only static force tasks. Our results strengthen their conclusion that CMC in gamma band is lower during static tasks than during dynamic tasks.

In case of the force tasks with multisines, frequencies in the gamma band with high CMC are probably harmonics of the perturbed frequencies, like in 34 Hz (harmonic of 17 Hz), 42 Hz (harmonic of 21 Hz) and 51 Hz (harmonic of 25 Hz shifted due to the band-pass filter). The presence of harmonics is a sign on non-linearity between EEG and EMG. Still no safe conclusion can be made on this due to the doubt on a direct corticomuscular connection during our experiment. It is more likely that the relation between perturbation and the brain and muscle activation is non-linear.

The drop in coherence when applying PRBS perturbation should be due to the change in the length of the muscles during the application of the perturbation. According to Riddle and Baker et al. [21], beta band synchronization arises only during isometric tasks and drops to non significant levels during movement.

In the end, it can be concluded that EEG activity is caused by proprioceptive information coming from Ruffini ending or muscle spindles in the wrist, while the EMG signal at the same frequencies is the result of spinal reflexes activating the flexing muscles. No conclusion can be made on the contribution of the pre-motor, primary motor, primary somatosensory and association somatosensory cortex on activation of the muscles through the analysis in frequency domain.

*Importance of longer trials.* As mentioned in section 2.3, we performed more trials with one subject (S1) when applying MS1, as well as PRBS1 perturbation, in order to assess the importance on having more segments to average over, while keeping the same length for each segment. The results of S1 in

the analysis of the data in frequency domain are not better than those from subjects 2 and 3, considering the frequency points that have CMC above the level of significance. The results in the same subject from MS2 perturbation are even better than those form MS1 perturbation.

In the same time, in the time domain analysis, improving the signal-to-noise ratio did result in a number of PEP but with low amplitudes. Subject 1 was the one with more identified PEP. Moreover, the reflexes in EMG could be identified more clearly in this subject S1.

Since this subject showed good results in both frequency and time domain analysis having longer trials than the others, we conclude that the number of trials do improve the coherence and PEP analysis. Moreover, during this attempt we noticed the benefit of applying PRBS perturbation, since as being a continuous signal, we didn't consume much time repeating the force task. In case of applying discrete pulses, the duration of the experiment would increase due to the lag in between the pulses.

Sources of corticomuscular coherence. By using DICS method, we could localize regions in the brain that showed coherent activation with the EMG channel above carpi radialis muscle. However, the value of the coherence between the dipoles in the brain and EMGflex channel is still low, even lower than CMC computed with Laplacian derivation. Our assumption that intracranial CSD might improve CMC acting as spatial filter didn't meet with the results from this analysis. Considering the location of the sources showing a low but above the level of confidence coherence with muscle activity, the results from the spherical and the realistically shaped models didn't match. In case of the spherical model this dipole was localized in the ispilateral primary somatosensory cortex close to the median line of the central sulcus, whereas in the realistically shaped model, two regions showed similarly hig results. One region is Broadmann area 38, which has an unknown functional significance, but it might bind complex, highly processed perceptual inputs to visceral emotional responses. The other one is the contralateral supplementary motor area in the parietal lobe of the cortex. From the top plot of Figure 14 though, it is indicated that this latter region may have slightly higher CMC than the supplementary motor area. However, since this region is not correlated with motor control, we assume that the supplementary motor area can more reliably explain the high CMC than this deep region in the brain. The latter results from the realistically shaped model are more plausible than with the sphereical model.

*Sources of early evoked cortical activity* Analysis in time domain was based on the study in [1]. In that study McKinnon et al. examined the location, magnitude and timing of the source generators of the cerebral potentials evoked by imposed

displacements of the human wrist and their relationship to the M2 response. They used discrete pulses to evoke PEP in the cortex. PRBS was used in our study in an effort to replicate these results. PRBS serves the benefit of being a continuous perturbation and saves more time than when applying discrete perturbations.

PEP found in the channels above the sensory-motor cortex didn't have similar amplitudes neither timing with the ones in [1]. However, this was expected due to the different perturbation signals applied in the two cases. When applying the spherical model to find the sources of the revealed PEP, we indeed found that three dipoles could explain the grand average of EEG for the time interval of early evoked activity, like in case of [1]. However, the accuracy of our results is not as high as in [1] since RV was higher in our case than in their case (7% in contrast to approximately 1.8%). Out of the three dipoles, two were found in locations very close to the location of one of their dipoles, lying above the contralateral primary cortex close to the central sulcus. However, when applying the realistically shaped model, the results were not similar. RV was quite low on dipole fitting of P/N50 potential found in some channels above the pre-motor and primary motor cortex. The dipole that was fitted was located approximately in the basal ganglia. Basal ganglia are a group of nuclei of varied origin that act as a cohesive functional unit. They are highly connected with the cerebral cortex and associated with a variety of functions, including voluntary motor control. Currently popular theories implicate that the basal ganglia are activated primarily in action selection, that is, the decision of which of several possible behaviors to execute at a given time. Experimental studies show that the basal ganglia exert an inhibitory influence on a number of motor systems, and that a release of this inhibition permits a motor system to become active.

*Comparison between spherical and realistically shaped models.* The reason for using two different head models in this study was to estimate the fidelity of a more complicated and data demanded model, as this is the realistically shaped model in contrast to a simple spherical model. It has been indicated that realistically shaped boundary element head models with uniform scalp and skull layer thickness and conductivity do not produce significantly more accurate EEG source localization than spherical models [55].

One problem while designing the realistically shaped model, besides its complexity, was the difficulty in fitting the electrode montage on it, due to its complex geomerty. This process was of course not a problem with the spherical model. Moreover, as long as the realistically shaped model is created by a template MRI, the results will be always biased, since the location of each electrode on the model will not match its real location during the experiment, due to the different head geometry of every subject.

Despites its apparent advantage in representing well the geometry of the head and the brain, the realistically shaped model didn't improve the results in coherence with DICS and in modeling the early evoked activity. However, the interpretation of the dipoles is only plausible in this kind of model, even if the lack in deep knowledge on neuroscience makes the interpretation of the identified brain regions quite subjective.

*Conclusion*.Considering the questions that were intended to be answered through this study, we can conclude on the following:

- There is a synchronization between the brain's and the muscles' activation mainly when applying a proprioceptive input. Because of the latter notice, no conclusion could be made on the nature of this communication on whether afferent signals, efferent signals or a combination of both contribute to this synchronization. CMC was high in the beta band, especially at 17 Hz and 29 Hz, whereas in the gamma band CMC is attributed to harmonics of exicted frequencies. Because of these harmonic, we can conclude that if a corticomuscular connection exists it should be non-linear
- No accurate conclusion could be made on the causality between EEG and EMG. The change in the sinus of the phase of CMC implies a non-causality, since the system should be a closed-loop system.
- There is an indication that the contralateral supplementary motor cortex has the most coherent with the carpi radialis muscle activity during wrist perturbation tasks. More data should be analyzed though so as to verify the latter finding.
- PRBS which is a continuous proprioceptive stimulus do cause an early cortical response. Identified PEP with an onset around 44 ms (termed here as P/N50) may contribute to the generation of the late reflexes in EMG, that had an average timing of 68 ms.
- The afore-mentioned evoked activity may be generated from the basal ganglia.

*Future recommendations*. Several comments about the experimental methodology followed during this project, as well as recommended changes to it, are presented in this section.

More base task trials of wrist perturbation should be held in order to verify the existence of CMC, expected to be higher in beta band. In the same time, by applying multisine perturbation, we expect to find an increase in CMC in frequencies that CMC was present during base taks, as well as in perturbed frequencies in which CMC below the level of significance in base task. This finding would strengthen our assumption that corticomuscular communication can be modeled as close-loop system, since afferent signals should contribute in the EEG activity in beta band.

Moreover, position tasks could be also held in order to verify on whether the afferent signals that generate EEG activity during perturbation tasks are cause from the muscle spindles or are cutaneous afferents. Multisine should be used again, since they proved very efficient in revealing coherence between structures.

PRBS proved to reveal PEP that could be recorded on the cortex. Therefore, more trials with PRBS with different stretch velocity should be applied. We expect to find PEP of different timing in case of a PRBS of different stretch velocity. Higher stretch velocities should elicit faster reflexes on EMG and faster PEP on EEG.

Anisotropic instead of isotropic conductivity values in the tissues of the realistically shaped model, by the use of Finite Element Model (FEM) instead of BEM might improve the results of an analysis with a realistically shaped model. FEM has been rarely applied to the EEG inverse problem due to technical difficulties such as availability of human head geometry, numerical complexity in mesh generation, and demanding computation. Using MRI to define the real boundary of the head, recent computer simulation studies in the FE head modeling and multiple source localization [56, 57] promise a better spatial resolution. In addition, combining and correlating fMRI and EEG via the realistic FE head model promises high spatiotemporal resolution for imaging the neural activity of the brain, enabling researchers to understand the precise temporal sequence and spatial extent of neuronal activity.

Finally, considering the intracranial CSD methods, sourceanalysis with minimum-norm application instead of dipole fitting could be performed to identify the sources of PEP. Minimum norm estimates [58] are based on a search for the solution with minimum power and correspond to Tikhonov regularization. This kind of estimate is well suited to distributed source models where the dipole activity is likely to extend over some areas of the cortical surface. Software packages, that implement minimu norm estimate is the MNE Suite that can be used in combination with FreeSurfer which is a package for creating a realistic mode of the cortex.

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#### APPENDIX A - HEAD MODELS

In Figure 21, the geometry of the spherical model, as well as the triangulations of the outer boundary (skin) of the realistically shaped model can be seen. The geometry of the rest two tissues (skull and brain) of the realistically shaped head model are plotted in Figure 22.



Figure 21. The geometry of the outer surface of the spherical head model (left plot) and the triangulated surface of the outer tissue (skin) of the realistically shaped head model (right plot).



Figure 22. The geometry of the skull tissue (left plot) and the corresponding of the brain tissue (right plot) of the realistically shaped head model.

APPENDIX B – WORK FLOW



#### APPENDIX C - RESULTS FROM TIME DOMAIN ANALYSIS

#### 1. Muscle reflexes in EMG



Figure 23.

EMG responses in the two channels (EMGflex, EMGext recording on the surface of flexor carpi radialis and extensor carpi radialis muscles) in all subjects. As mentioned in the report, subject 2 shows no reflexions, whereas for subjects 1 and 4 distinguishing two peals (M1 and M2) in the early activity of EMG is more clear.

#### 2. Baseline correction in subject



Figure 24.

In the plot we can see evoked potentials left after baseline removal in subject 1. Every non-zero activity can be considered as PEP due to PRBS1 perturbation. In that way, PEP were defined in section 3.3 of the report.

|           | TABLE IV       |                |               |
|-----------|----------------|----------------|---------------|
| Subjects  | Dipole 1       | Dipole 2       | Dipole 3      |
| S1        | -2 1 -7 (CPM)  | 2 0 2 (CPrM)   | -2 1 -8 (CPM) |
| <i>S2</i> | 2 -4 -7 (IPrM) | 14-2 (CPrM)    | 16-6 (CPrM)   |
| \$3       | -1 -8 0 (IPM)  | 0 6 -2 (CPrM)  | 0 7 -3 (CPM)  |
| 54        | -1 -3 -7 (IPM) | 0 -3 -3 (IPrM) | -2 0 1 (CPM)  |
| <i>S5</i> | -2 -5 -6 (IPM) | 1 4 -2 (CPrM)  | 1 7 -3 (CPrM) |

APPENDIX D – TABLE OF THE LOCATION OF DIPOLES IN THE SPHERICAL HEAD MODEL

Locations in the cortex of the three dipoles that model the ERPs activity in every subject. CPrM: contralateral pre-motor cortex. CPM: contralateral primary motor cortex. IPrM: ipsilateral pre-motor cortex. IPM: ipsilateral primary motor cortex