The longitudinal relation between EEG evoked by wrist perturbations and upper limb motor recovery in sub-acute stroke

Jessica E. Wijngaarden

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Master of Science in Biomedical Engineering

Delft University of Technology

Student number: 4731255

Supervised by: Dr. ir. Alfred C. Schouten
Dr. Joost van Kordelaar

Abstract

Introduction Stroke often initially leads to motor impairments of the upper limb. The largest improvements in recovery take place during the first half year after stroke. With more knowledge about neurological recovery, it may be possible to predict motor recovery after stroke with the use of neurological biomarkers. Prediction of stroke recovery can be used in the selection and development of rehabilitation therapies. By applying continuous perturbations to a joint with the use of a robotic manipulator during different control tasks, the evoked cortical responses of the sensorimotor cortex can be studied. With this method, evaluating the relation between EEG activity and motor function of the upper limb may provide meaningful EEG biomarkers for motor recovery after stroke.

Methods A selection of 13 sub-acute stroke patients who participated in the 4D EEG project were longitudinally measured four times during the first half year after stroke. EEG was measured during relax, position and force tasks while a robotic wrist manipulator applied continuous perturbations to the affected wrist. The upper limb part of the Fugl-Meyer assesment (FMA) was used to asses the upper limb motor function. The index of the signal-to-noise ratio (iSNR) was obtained from the EEG data.

Results The FMA score was strongly related to time post stroke. Also, FMA score during the first measurement was lower than during the second, third and fourth. The iSNR was lower during the position task than during the relax and force tasks. A moderate relation was found between the FMA score and the iSNR during the position task, but not during the relax and force task.

Conclusion The iSNR during the position task is potentially a EEG biomarker for upper limb motor recovery after stroke.

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1 Introduction

Stroke is the second leading cause of death and the third leading cause of disability around the world [1], which makes it a worldwide concern. Every year, there are globally 15 million stroke survivors [2]. In approximately 80 percent of these survivors, stroke leads to motor impairments of the upper limb [3, 4]. Due to these motor impairments, stroke patients have trouble with daily activities and social participation, which decreases their health-related quality of life [5, 6].

Recovery of body functions after stroke typically follows a logarithmic pattern, in which the largest improvement takes place in the first hours until weeks after stroke [7–9]. For example, van Kordelaar et al. [10] found that the ability to perform dissociated movements again of the upper limb occurs in the first 5 weeks after stroke. Studying neurological recovery would therefore be most interesting if both brain activity and functional recovery are measured repeatedly, starting in the first days after stroke until functional recovery has reached a plateau [7]. With more knowledge about neurological recovery, it may even be possible to predict functional recovery after stroke with the use of neurological biomarkers. Prediction of functional recovery after stroke is beneficial in the selection and development of rehabilitation therapies [11].

Electro-encephalography (EEG) is a suitable neuro-imaging technique in the clinical setting to investigate neurological recovery after stroke. EEG measures brain activity with high temporal resolution, is non-invasive and low-cost [12]. The high temporal resolution of EEG makes it possible to assess the brain activity in response to movement and other stimuli [13]. Compared to other brain imaging techniques, such as functional magnetic resonance imaging and magnetic-encephalography, EEG is more practical because it can be measured at any location. As EEG is already part of standard practice, EEG biomarkers have a high potential to be used in clinical practice, and obtaining EEG biomarkers is shown to be feasible in the acute stroke phase [14, 15].

1.1 Problem statement

EEG activity has previously been related to recovery in sub-acute stroke patients in order to find EEG biomarkers. Literature about quantitative EEG measures have shown that the delta/alpha ratio [16], the (delta+theta)/(alpha+beta) ratio [17], the pairwise derived brain symmetry index [17], relative alpha power [16] and delta power [18] at baseline correlated with recovery months after stroke. Another study showed that higher interhemispheric synchrony within seven days after stroke related to better motor recovery at two months after stroke [19]. Also, Nicolo et al. [20] found that the coherence between the ipsilesional primary motor cortex and the rest of the cortex at 2-3 weeks was related to improvements in upper limb motor function three months after stroke. However, all these studies measured EEG during resting state. It is therefore unclear what neurological processes are responsible for the recorded EEG activity. By studying EEG in sub-acute stroke patients in response to certain stimuli, the meaning of the found EEG activity can be derived and the processes in the brain during motor recovery after stroke can be studied.

Cortical damage due to a stroke impairs motor control by means of altered feed-forward and feedback control. Research has already been done into the affected feed-forward control, which is thought to result in unusual motor synergy patterns and muscle weakness [7, 21–23]. Feedback control requires connection between the

somatosensory receptors in the periphery and in the sensorimotor cortex. There is less known about this altered sensory connection between the periphery and cortex in stroke patients [21] and how this is related to motor recovery. By applying continuous perturbations to a joint with the use of a robotic manipulator, the evoked cortical responses of the sensorimotor cortex can be studied [24], which gives information about the sensory pathways. Studying EEG activity in response to these joint perturbations would potentially provide meaningful EEG biomarkers.

Different control tasks can be executed during those measurements. During a relax task, the instruction is to not react on the perturbations applied to the joint. The aim of a force task is to maintain an isometric force while the perturbations are applied, while during the position task the aim is to maintain a certain angle of the joint [25]. Those tasks can be considered to have different difficulty in terms of control and may evoke different cortical activation. In healthy patients, solely somatosensory cortical activation will be expected during the passive relax task, because of the sensory feedback. The active position and force task are expected to also evoke motor activity in the cortex, as these tasks require motor activity around the joint. There also seems to be differences in cortical activity between the position and force task. Poortvliet et al. [26] found less cortical involvement during position control knee extension tasks in healthy people than during force-control tasks.

In the 4D EEG project, from which the participants were selected for this study, EEG was repetitively measured in stroke patients during the first half year post stroke while those three control tasks were performed. An customized measurement van was used to measure the patients at their location. Previous cross-sectional literature [21,27] has also researched the cortical activity in response to continuous disturbances of the wrist joint during the relax and force tasks in stroke patients. These studies found that this method is adequate in assessing the integrity of the sensory pathways in stroke patients and that valuable information can be extracted from the data in understanding recovery after stroke. However, no literature was found that compared between all three tasks. Additionally, the cortical activity during different control tasks has not yet been studied longitudinally in sub-acute stroke patients, while this would be most valuable in discovering new EEG biomarkers for motor recovery after stroke.

1.2 Goal

In order to fill the gap in the literature, the differences in cortical activity between the three control tasks in response to continuous perturbations of the wrist will be studied longitudinally in patients during the first half year (sub-acute) after stroke. The long-term goal would be to have a neurological biomarker able to predict motor recovery early on after stroke. Therefore, the goal of this study is to evaluate during which control task the index of the signal-to-noise ratio (iSNR), obtained from EEG data, may be a EEG biomarker for upper limb recovery after stroke. In order to verify the possibility of the iSNR to be a EEG biomarker, the correlation between iSNR and motor recovery of the upper limb after stroke, measured with the Fugl-Meyer motor assessment (FMA), will be evaluated during the three control tasks. The research question of this study is: *What is the relation between the iSNR and FMA score longitudinally measured in sub-acute stroke patients while performing three different control tasks (relax, force and position task)?*

2 Methods

2.1 Patient information

The participants of this study were selected from the 4D EEG project. For this project, 49 stroke patients were repetitively measured during the first half year after stroke onset. The patients performed different control tasks (relax task, position task and force task) with use of a robotic wrist manipulator during which EEG was measured. This was done four times; at 1, 2 or 3 weeks (this differs between patients), at 5, 12 and 26 weeks after stroke. Additionally, clinical measures were assessed in the same four weeks.

For inclusion into the project, the following inclusion criteria were used; (i) first-ever ischemic stroke in the anterior, middle and/or posterior cerebral artery less than 3 weeks ago, (ii) paretic upper limb (NIHSS 5a/b: $4 \leq \text{score} > 0$), (iii) age $\geq$ 18 yr, (iv) no severe cognitive deficits (mini mental state examination score $\geq$ 20), (v) able to sit upright independently. The exclusion criteria were: (i) other neurological disorders, (ii) pacemaker or other metal implants, (iii) orthopedic limitations of the paretic upper limb that influenced movements before the stroke, (iv) use of botulinum-toxin injections or other medication that influence the upper limb in the last 3 months.

All participants gave written informed consent for participating in the project. Procedures were approved by the Medical Ethics Reviewing Committee of the VU Medical Center, Amsterdam (protocol number 2014.140, Dutch Central Committee on Research Involving Human Subjects, CCMO, protocol number NL47079.029.14) and were conducted in accordance to the Declaration of Helsinki.

For this study, the goal is to compare the relax, position and force task longitudinally. Therefore, only 13 patients who completed all three tasks at least three out of four times (see Figure 6 in the appendix) were included in this study (1 female, age 64.6±12.9). The other 36 patients that participated in the 4D EEG project were excluded from this study due to missing data, because they were not able to perform all three tasks at least three out of four times. The relax tasks was completed 80% of the time, the force task 50% and the position task only 40% (see Figure 6). The patient characteristics are shown in Table 1.

Table 1: Patient characteristics sorted by FMA score in week 1/2/3.

Patient	Age	Sex	FMA wk 1/2/3	wk 5	wk 12	wk 26	Affected side
1	54	M	1: 15	44	59	62	right
2	62	M	2: 18	49	56	60	right
3	58	M	3: 20	25	39	51	right
4	43	M	3: 21	24	44	58	left
5	79	M	1: 34	55	58	57	left
6	72	M	2: 35	54	59	60	left
7	86	F	1: 36	62	62	63	right
8	58	M	3: 38	53	61	63	left
9	63	M	1: 39	62	62	64	right
10	77	M	3: 49	60	62	63	left
11	73	M	2: 55	59	60	60	left
12	46	M	2: 60	66	66	66	left
13	69	M	1: 65	66	66	66	left

2.2 Clinical assessment

Prior to inclusion into the study, the National Institutes of Health Stroke Scale (NIHSS) was assessed [28]. The paretic upper limb was assessed with item 5 a/b of the NIHSS about the motor function of the upper limb which resulted in a score between 0 and 4. The mini mental state examination which was assessed for inclusion into the study consisted of 19 questions resulting in a score between 0 and 30. The questions concerned orientation of time and place, language, memory, concentration and praxis.

Clinical assessment of motor recovery was done at the same four moments as at which the motor tasks were executed. Motor recovery of the upper limb was assessed using the upper limb part of the Fugl-Meyer motor assesment (FMA). The FMA was specifically designed to measure sensorimotor recovery after stroke and is widely used in the stroke population. The test is a 3-point Likert type scale and consists of 5 domains: motor function, sensory function, balance, joint range of motion and joint pain. The upper limb part of the motor function domain was used for this study and results in a numerical score between 0 and 66 [29]. The results are presented in Table 1.

2.3 Experiment setup

Depending on the location of the patient, control task measurements were done in the hospital or in a customized measurement van (Volkswagen Crafter, Wolfsburg, Germany) that drove to the patients' home. The van was equipped with a wheelchair (Ibis, Sunrise Medical Incorporated, Fresno, CA, USA), stabilizing feet, curtains, a wheelchair lift, shaded windows, EEG equipment and the robotic wrist manipulator (Figure 1a).

The affected arm was fixed to the robotic device using Velcro straps such that no active grip was required from the patient (Figure 1b). The wrist joint was aligned to the axis of the motor. Due to the shape of the handle, the forces were applied to the palmar surface of the hand without the fingertips holding the handle. A computer monitor was placed in front of the patients showing a circle during the relax task, and with an arrow giving task related feedback during the force and position tasks (Figure 1c). Correlation between eye movement and the perturbation signal was prevented by low-pass filtering the visual feedback signals (cut-off frequency of 0.6 Hz).

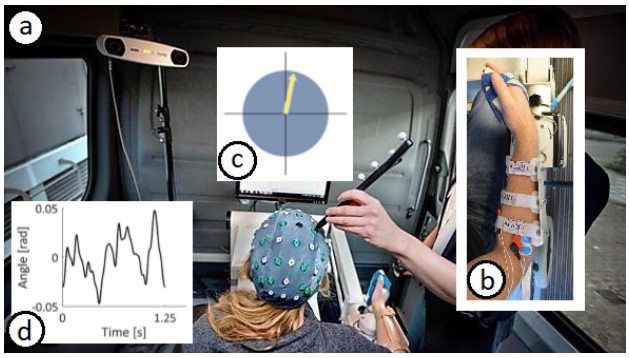


Figure 1: Measurement van (a), Wristalyzer (b), visual feedback (c) and perturbation signal (d).

2.3.1 Recording system

All signals were recorded during the control tasks using a Refa amplifier (TMSi, Oldenzaal, The Netherlands) at a sample rate of 2048 Hz. EEG was measured with a 64 Ag/AgCl electrodes cap arranged according to the 10/20 system. A ground electrode (Blue Sensor N, Ambu Ballerup, Denmark) was fixed to the left mastoid process of the patient. The applied and recorded angle and torque signals from the robotic wrist manipulator were measured with optical isolation amplifiers (TMSi) to ensure the safety of the patient.

2.3.2 Control tasks

Control tasks were executed while continuous periodic angular perturbations were applied to the paretic wrist in palmar- and dorsiflexion with use of a robotic wrist manipulator (Wristalyzer, MOOG, Nieuw-Vennep, The Netherlands) [21]. During all three tasks, the perturbations were applied around a neutral position of 20°wrist palmar flexion, allowing comparisons between patients and tasks.

During the passive relax task, the patients were instructed to relax their wrist while angular perturbations were applied around the neutral wrist position. No task related feedback was given during the relax task. During the active force task, the patients were instructed to maintain a constant force of 20% of their maximum voluntary contraction (MVC) while the angular perturbations were applied. Visual feedback was given on a computer screen in front of the patient. During the active position task, instructions were to maintain the neutral position of the wrist while the perturbations were applied. The same visual feedback was given as during the force task.

The MVC of the paretic arm during wrist flexion was measured. The robotic wrist manipulator was used to measure MVC in patients with a wrist flexion torque lower than 5 Nm. For stronger patients, a handheld force transducer (MicroFet, Draper, UT, USA) was used to measure the MVC. During the test, the patients were verbally encouraged to put in maximal effort.

All patients did 4 measurement sessions (week 1, 2 or 3, week 5, week 12 and week 26). During each session, the relax task was executed first, then the position task and thereafter the force task, if possible. For each task, 20 trials were recorded. One trial consisted of 10 repetitions of the perturbation and lasted 12.5 s. To prevent fatigue, there was a break of at least 5 s between trials.

2.3.3 Perturbation signal

During all three tasks, the same periodic continuous angular perturbation signal was applied to the wrist (Figure 1d). This signal was a multisine signal with random-phase (e.g. the sum of multiple sinusoids, each with a random phase [30]). In choosing the period of the signal, a trade-off was made between the number of periods to be recorded during one session and the frequency resolution, having more periods results in a better estimation of the average response. Also, the ability of the upper limb to control movements at high frequencies is limited due to the inability of muscles to contract at high rate and due to the inertia of the limb [31]. Therefore, the signal had a period of 1.25 s (frequency resolution: 0.8 Hz), so that it could contain low frequencies. The multisine signal consisted of sinusoids with the following frequencies: 0.8, 1.6, 2.4, 3.2, 4.0, 4.8, 5.6, 6.4, 8.0, 9.6, 11.2, 13.6, 16.0 and 19.2 Hz.

The frequencies lower than the natural frequency of the wrist (3 to 5 Hz in relaxed state) had the highest amplitudes, because reflexes are most effective at low frequencies due to the time delay associated with them. Frequencies above 4 Hz were decreased in amplitude. Firstly, because the required forces to manipulate the wrist above the natural frequency increase quadratically with increasing frequency, which the robotic manipulator is not capable of. Secondly, muscle spindles are sensitive to velocity changes. So in order to manipulate them equally over all frequencies, the amplitude of the signal should be decreasing over frequency giving the perturbation a flat velocity spectrum [31, 32]. To generate similar palmar and dorsiflexion as in patients with a paretic right wrist, the perturbation signal was mirrored for patients having a paretic left wrist [21].

2.4 Data analysis

Data analyses were done in MATLAB R2018b (The Mathworks, Inc., Natick, Massachusetts, United States) and with the use of the toolboxes Fieldtrip (version 2018-09-23) [33] and EEGLAB (version 14.1.2b) [34].

2.4.1 Preprocessing

Fourth order butterworth filters were used to band-pass filter the EEG trial data between 0.8 Hz and 120 Hz and to band-stop filter around 50 Hz and 100 Hz to remove line noise and its harmonic. In order to prevent excessive noise to influence the data, an algorithm was used to remove channels with too much noise (see Appendix D). The remaining EEG channels were re-referenced to the common average.

Thereafter, the 20 trials (each 12.5 s) were divided into 10 epochs of 1.25 s, aligned to the period of the applied perturbation signal. Of each trial, the first two epochs were rejected to reduce risk of transient effects. This resulted in 160 epochs per task. In order to prevent excessive noise to influence the data, an algorithm was used to remove epochs with too much noise (see Appendix D). When less that 60 epochs remained, the task was excluded from the analysis.

2.4.2 Independent component analysis

To remove artifacts from the data, an independent component analysis (ICA) was done using the Infomax algorithm in runICA. ICA was performed on the EEG data of all three control tasks combined. Independent components (ICs) were defined as muscle artifacts if the power in the power spectrum increased with increasing frequency. ICs representing blinking and eye movement artifacts were detected based on their topographical representation and the signal in time domain. ICs with a residual variance of more than 15% or ICs mainly resulting from one electrode were also excluded from the data. The remaining ICs were considered to represent brain activity and were back projected to electrode level. Thereafter, the second-order derivative (the surface Laplacian) of the EEG data distribution was calculated to minimize the influence of volume conduction and to improve spatial resolution [35]

2.4.3 Signal-to-noise ratio

The processing of sensory pathways was assessed with the steady state response (SSR). The SSR is calculated for each electrode and is the average cortical response over all epochs:

$$\hat{x}(k) = \frac{1}{P}\sum_{p=1}^{P} x^{[p]}(k) \tag{1}$$

where $\hat{x}$ is the SSR, x is the recorded signal from one electrode, k is a sample in a epoch p, and P is the total number of epochs [21].

Due to differences for example in scalp conductivity, the magnitude of the signal varies between patients. To be able to compare between patients and tasks, the signal-to-noise ratio (SNR) was calculated. The power of the SSR was divided by variance across the epochs, which resulted in the SNR per electrode:

$$SNR = \frac{\hat{E}_x}{\hat{\sigma}_x^2} = \frac{\sum_{k=1}^{N} \hat{x}(k)^2}{\sum_{k=1}^{N} \frac{1}{P-1} \sum_{p=1}^{P} \left(x^{[p]}(k) - \hat{x}(k)\right)^2} \tag{2}$$

After filtering and rejection of artifacts, the variance across epochs is assumed to be mainly background brain activity, uncorrelated to the perturbation signal [21]. In the SNR, the signal is the average response across epochs to the perturbation and the noise is the variance across epochs.

2.4.4 Index of the signal-to-noise ratio

From the SNR, the index of signal-to-noise ratio (iSNR) was calculated. The iSNR compares the SNR of one electrode (SNR_{ROI}) to the average SNR of the 20 electrodes with the lowest SNR (SNR_{rest}). The SNR_{ROI} electrode is the one of the nine electrodes in the region of interest (ROI) with the highest SNR. The electrodes included in the region of interest are: FC1, FC3, FC5, C1, C3, C5, CP1, CP3, CP5 for a left-sided brain lesion and FC2, FC4, FC6, C2, C4, C6, CP2, CP4, CP6 for a right-sided brain lesion, which represent the ipsilesional sensorimotor cortex. The iSNR was calculated with:

$$iSNR = \frac{SNR_{ROI} - SNR_{rest}}{SNR_{ROI} + SNR_{rest}} \tag{3}$$

The iSNR results in a ratio between -1 and 1, where 1 indicates only activation in the ROI.

2.5 Statistical analyses

A Spearman's correlation was done to evaluate the relation between FMA score and weeks after stroke. Also, a Friedman's ANOVA was used to examine the change in FMA over the four different measurements. For analyzing the differences between the three tasks in iSNR over measurement, a factorial repeated measures ANOVA was conducted. Additionally, a linear mixed model analysis with repeated measures was conducted with measurement and task as fixed factors. In order to validate the possibility of the iSNR of being a biomarker, its Spearman's correlation with FMA score was examined for all three tasks. In case of significant main effects, post hoc testing was done. All significance levels were set to α=0.05. All statistical analyses were done using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) [36].

3 Results

3.1 FMA score over time

Figure 2 shows the FMA scores over time after stroke per patient. A Spearman's correlation test showed a statistically significant strong correlation between FMA score and time after stroke ($r(50)=0.56$, $p< 0.001$). Additionally, the Friedman's ANOVA showed statistically significant differences in FMA score between the four measurements ($\chi^2(3)=35.2$, $p< 0.001$). Post hoc Bonferroni testing showed that the FMA score during the first measurement (mean±SD: 37.3±16.3) was statistically significantly lower than the FMA score during the second (52.2±13.9), third (58.0±7.9) and fourth measurement (61.0±4.1), with $p=0.015$, $p< 0.001$ and $p< 0.001$ respectively. Also, FMA score during the second measurement was significantly lower than during the fourth measurement, with $p=0.003$.

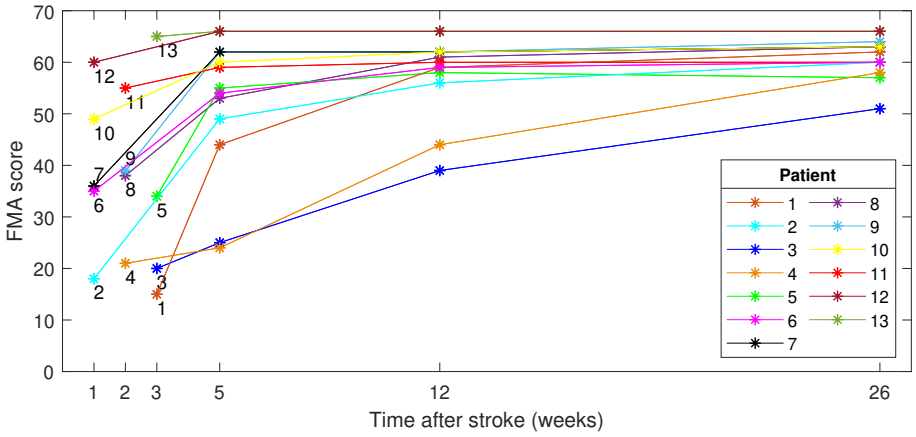


Figure 2: FMA score plotted against time after stroke for all patients (n=13).

3.2 SNR and iSNR

The SNR topographical plots were averaged across all patients for each task and measurement (see Figure 3). The averaged iSNR across all patients are shown in Figure 4. A factorial repeated measures ANOVA showed a statistically significant main effect of task on the iSNR ($F(2,10)=10.14$, $p=0.004$). There was no statistically significant main effect of measurement or interaction effect found on the iSNR ($F(3,15) = 1.23$, $p=0.33$ and $F(6,30)=0.52$, $p=0.79$). Post hoc testing using Tukey's honest significant difference criterion showed that the iSNR during the position task (0.60±0.13) was statistically significantly lower than during the relax (0.68±0.11) and the force task (0.69±0.15), with $p=0.001$ and $p=0.025$ respectively.

Results from the linear mixed model analysis are as follows. Changing the covariance structure from a diagonal structure to a heterogeneous first-order autoregressive structure, which assumes correlations between repeated measures to be higher at adjacent time points [36], significantly improved the model fit, $\chi^2(1)=124.7$, $p< 0.001$. There was a statistically significant main effect found for task ($F(2,71.2) = 19.3$, $p< 0.001$), but not for measurement ($F(3,71.2) = 0.57$, $p=0.64$) nor an interaction effect ($F(6,40.7)=0.51$, $p=0.80$). Post hoc Bonferroni testing showed that iSNR during the position task (0.59±0.19) was statistically significantly lower than during the relax (0.65±0.20) and force task (0.69±0.17), with both $p< 0.001$.

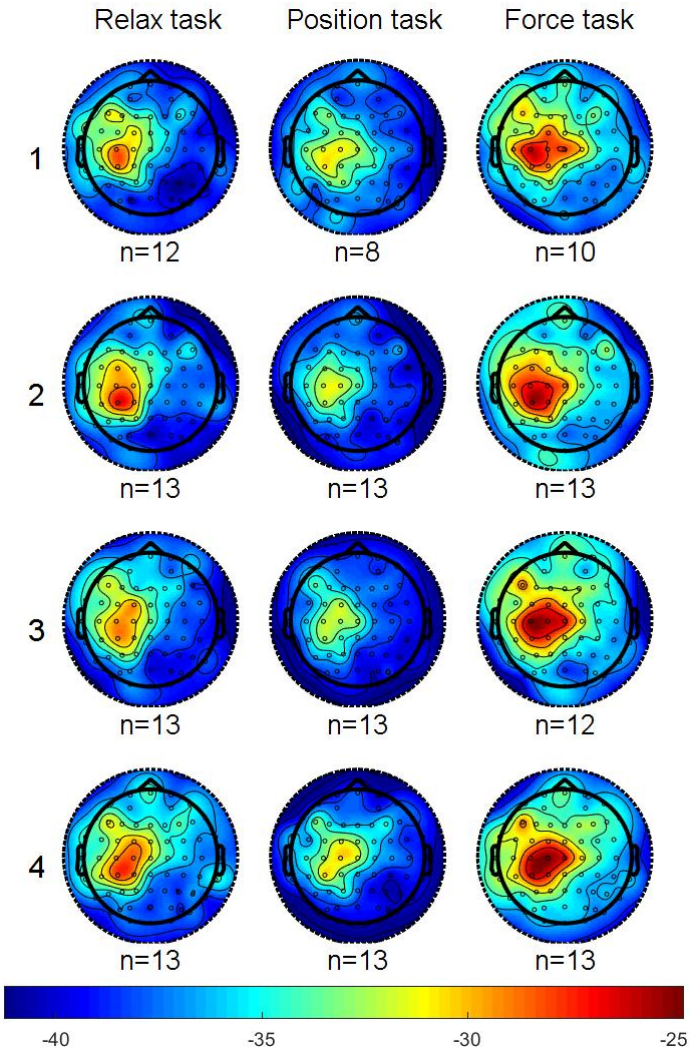


Figure 3: Average SNR plotted in dB for the different tasks and four measurements. The n indicates the number of patients. Results corresponding to perturbations applied to the left wrist were mirrored with respect to the sagittal plane, such that the left side in the figures is contralateral to the perturbation.

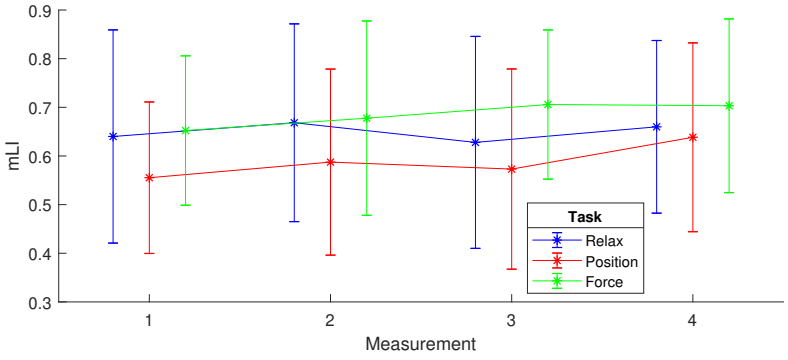
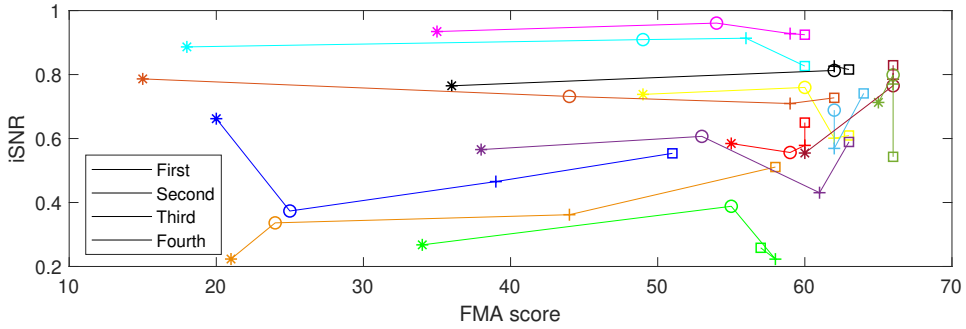


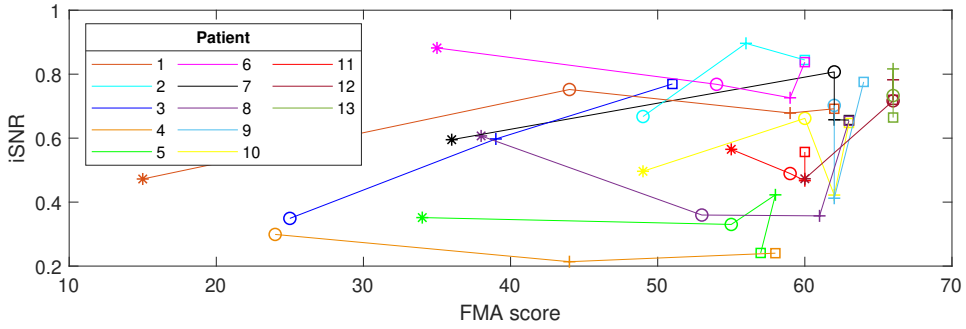
Figure 4: The iSNR averaged over all patients and standard deviations for the different tasks and four measurements.

3.3 Relation between iSNR and FMA score

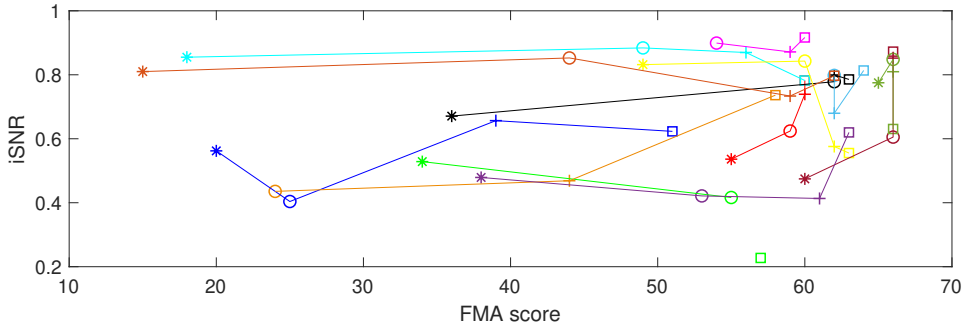
The iSNR was plotted against FMA score for all three tasks in Figure 5. A Spearman's correlation test showed a statistically significant moderate positive correlation between iSNR and FMA score during the position task (r(45)=0.37, p=0.01) (see Figure 5b). However, no statistically significant correlations were found between iSNR and FMA score during the relax (r(49)=0.23, p=0.11) and the force task (r(46)=0.22, p=0.14) (see Figures 5a and 5c).



(a) Relax task



(b) Position task



(c) Force task

Figure 5: The iSNR plotted against FMA score for all patients (n=13) for the relax (a), position (b) and force (c) task. The asterisks indicate the first, the circles the second, the plusses the third and the squares the fourth measurement.

4 Discussion

The goal of this study was to evaluate if the iSNR may be a EEG biomarker for upper limb motor recovery after stroke during different control tasks. There was a strong relation found between FMA score and time after stroke. Also, the FMA score differed over time; FMA score during the first measurement was lower than during the second, third and fourth measurement; and FMA score during the second was lower than during the fourth measurement. The iSNR was lower during the position task than during the relax and force task. There were no differences found in iSNR between the different measurements. The iSNR measured during the position task was found to be related to FMA score after stroke. This relation was not found in the relax and force tasks.

4.1 Improvements in FMA score over time

In this study, the FMA was used to measure the upper limb motor recovery. In literature about recovery after stroke, there exists ambiguity in the definition of recovery. The term "recovery" is used in cases where the execution of upper limb movements is the same as before stroke, so the muscles and joints are used in the same manner; true motor recovery. However, the term "recovery" also is used to refer to cases where patients for example use their trunk during reaching movements to compensate for the motor impairment of their upper limb in order to reach their goal [37, 38]; motor compensation. The upper limb part of the FMA examines the restoration of body functions by directly measuring the motor impairment [7]. The FMA assesses the quality of movement performance and does not concentrate on functional outcome. Thus, the FMA only assesses true motor recovery of the upper limb and it does not allow motor compensation.

To be able to find a relation between the iSNR and the FMA score, there should be enough variability in FMA score. Fortunately, this is the case; FMA score varied from 15 in the first measurement to a maximum of 66 in the fourth measurement (see Table 1). The logarithmic pattern of the FMA score over time found in this study (see Figure 2) is in agreement with results in previous studies [8–10, 39]. Regardless of the initial FMA score, the greatest improvement in FMA score takes place in the first weeks after stroke. Thereafter, true motor recovery continues until about 12 weeks after stroke when the FMA score reaches a plateau.

4.2 Differences in SNR and iSNR between control tasks

To the best of our knowledge, this study was the first to longitudinally compare EEG activity between a relax, position and force task in the sub-acute stroke phase. Before comparing between control tasks, it is important to understand what the iSNR represents. The iSNR is calculated from the electrode with the highest SNR in the ipsilesional sensorimotor cortex divided by the SNR at rest, namely the average SNR of 20 electrodes with the lowest SNR. The iSNR is therefore an indication of the amount of activity in the ipsilesional sensorimotor cortex in response to a perturbation. As the SNR assesses the amount of cortical activity that relates to a perturbation signal applied at the periphery, the iSNR is a measure for the integrity of the sensory pathways. Results from this study show that the iSNR during the position task is lower than during the relax and force tasks. However, this doesn't mean that the anatomical integrity of the sensory pathways was different during the different tasks, because these three control tasks were executed by the same patients

during the same measurements. The explanation for the differences between control tasks may be in the way the iSNR is obtained.

During the position task, the wrist has to maintain a certain position by decreasing its admittance. This can be done with two different strategies; proprioceptive feedback and co-contraction. With proprioceptive feedback, perturbations are detected and muscles will provide restoring forces. The other strategy, co-contraction of the muscles, is constant contraction of antagonistic muscles around the wrist joint to stiffen the joint [40]. The strategy of proprioceptive feedback is a direct reaction to the applied perturbation, so cortical activity patterns similar to the perturbation signal are expected to be found. This is in contrast with the strategy of co-contraction, where the cortical activity is not expected to be related to the applied perturbation signal. Eventually, the iSNR is calculated from the SNR, which assumes a repeated cortical activity over all trials as response to the perturbation. Proprioceptive feedback will contribute to the amount of signal, while co-contraction will contribute to the amount of noise. Therefore, the proprioceptive feedback would result in higher SNR and iSNR while the co-contraction strategy would not.

During the force task, the admittance of the wrist has to be increased to give weigh to the applied perturbations. For the force task, as well as for the relax task, only proprioceptive feedback is used; the applied perturbations are detected by the muscle spindles and these signals are fed back to the cortex. During the position task, both perturbation-related and -unrelated cortical activity is expected, while during the force and relax task, only perturbation-related cortical activity is expected. This would result in the force and relax tasks to elicit higher SNR and the position task to elicit lower SNR, which explains the results from this study. Following this line of thinking, the perturbation-related cortical activity is expected to be higher during the force task than during the relax task. For the relax task, there is no interference from the patient, the cortical activity would represent solely the passive reaction to the perturbation. During the force task, the patient has to maintain a constant force, meaning that the active reaction to the perturbation will be augmented. This would results in higher perturbation-related cortical activity, and therefore higher SNR and iSNR than during the relax task. Even though there were no significant differences found in iSNR between the relax and force task, the iSNR during the force task tended to be higher than during the relax task (see Figure 4).

Previous cross-sectional literature about EEG during robotic continuous joint manipulation in stroke patients also found slightly higher cortical activity during the force task compared to the relax task. Campfens et al. [27] studied the cortical activity in stroke patients in the sub-acute phase while performing a relax and force task with the affected and non-affected wrist. The presence of coherence between the applied position perturbation and cortical activity (PCC) in the ipsilesional sensorimotor cortex tended to be higher during the force task performed with the affected wrist compared to the relax task [27]. However, Vlaar et al. [21] studied the SNR during a force task and a relax task in chronic stroke patients assigned to four different sensory impairment groups (severe, mild, none and control) and found contrasting results. The SNR was found to be lower during the force task than during the relax task in the mild sensory impairment group, and no significant differences were found for the other groups [21]. This difference in results may be explained by the fact that only one patient from this study would be assigned to the mild sensory group in all four measurements and four only partly, while most (8

out of 13) of the participants from this study would be assigned to the no sensory impairment group in all four measurements (see Figure 7 in the appendix). The results from this study should therefore be compared to the results from the no sensory impairment group. Though not significant, the SNR tended to be higher during the force task compared to the relax task in the no sensory impairment group [21], which is in agreement with the results from this study.

4.3 No differences in iSNR between measurements

The iSNR did not differ between measurements. This can be explained by the high variability in FMA scores during the different measurements, especially for the first measurement where the lowest FMA score was 15 and the highest was 65. Since the iSNR is thought to be related to FMA score, as found during the position task, the iSNR would not differ between measurements with high variability in FMA scores. More importantly, the presence of differences in iSNR between measurements is actually not relevant. Stroke patients show high variability in recovery patterns and outcome [7]. It is therefore important to consider how the brain activity relates to functional outcome, such as the FMA score, instead of how it changes over time.

4.4 Relation between iSNR and FMA score

The found relation between iSNR during the position task and FMA score in sub-acute stroke patients shows that the iSNR may possibly be a biomarker for motor recovery after stroke. The SNR assesses the amount of cortical activity that relates to the applied perturbation signal at the periphery and thus is a measure for the integrity of the sensory pathways. The moderate positive correlation found between iSNR and FMA during the position task would therefore indicate that a higher activity in response to a perturbation in the ipsilesional sensorimotor cortex, which indicates better integrity of the sensory pathways, is associated with better motor function of the upper limb.

The relation between iSNR and FMA score are in accordance with results from previous cross-sectional literature. Campfens et al. found that the PCC in the ipsilesional sensorimotor cortex, comparable to the iSNR, was higher in stroke patients with good motor function than in patients with poor motor function [27]. Additionally, Vlaar et al. [21] found higher SNR in the ipsilesional sensorimotor cortex for the mild and no sensory impairment and control group during the relax task, and for the no sensory impairment and control group during the force task [21]. However, the severe sensory impairment group did not show this lateralization in SNR in either task. This could be due to that Vlaar et al. [21] studied stroke patients in the chronic phase instead of the sub-acute phase. According to the results of this study, higher activity in the ipsilesional sensorimotor cortex relates to better motor function. The absence of lateralization in SNR in patients with severe sensory impairments in the chronic phase may indicate that they have no recovery in prospect, since most of the recovery would have already taken place during the sub-acute phase.

The presence of co-contraction strategies during the position task, which are not expected during the force and relax task, may also explain why there was no relation found between the iSNR and FMA score during the relax and force tasks. Previous literature found that stroke patients show high levels of spastic co-contraction [41, 42]. Therefore, patients with lower FMA scores may tend to use co-contraction more often during position tasks, which would result in lower iSNR.

This would explain why lower FMA scores are related to lower iSNR. This relation would not be expected during the force and relax task, since co-contraction is not expected during those tasks.

The association between better integrity of the sensory pathways and better motor function is also in line with literature about motor learning. Recovery of motor function can be compared to learning new motor skills, because the mechanisms active in the brain during spontaneous stroke recovery, during the sub-acute phase, are similar to those during motor learning [43]. In accordance with results from this study, sensory input is critical in the acquisition of new motor skills and in the recovery after brain injury [44] as demonstrated in a study with monkeys. Due to a lesion in the hand area in the somatosensory cortex of one hemisphere, the monkeys experienced difficulties in learning new skills with the ipsilesional hand [45]. Additionally, several studies have shown that sensory stimulation of the paretic upper limb is beneficial for functional recovery after stroke [46–48]. The integrity of the sensory system thus seems to be important in motor recovery after stroke.

4.5 True neurological recovery or compensation?

The difference between true recovery and compensation as described in Section 4.2 is also present on the neural level. True neurological recovery would refer to restitution or repair of the damaged areas in the brain. However, actual repair of neurons at the primary area of the lesion is probably not possible [49]. Restitution of damaged areas might occur in the penumbra, which are the areas closely around the lesion that suffer from the lesion but in which the damage is (partially) reversible [38, 49]. Therefore, true neurological recovery is defined as restitution of brain function of the penumbra. Neurological compensation refers to activation of areas in the brain that are normally in that situation not active in healthy individuals [38].

One important question in research about recovery after stroke is whether true neurological recovery or neurological compensation has taken place. To answer that question in the context of the results from this study, the found relation between iSNR and FMA score during the position task should be considered. Better FMA scores, so better motor function, were found to be related to higher iSNR. This suggests that the iSNR would increase with true motor recovery. The results from this study, higher SNR in the ipsilesional sensorimotor cortex along with the positive iSNR, indicate activity in the ipsilesional sensorimotor cortex and not in other areas of the brain. Therefore, it is not possible that the improvements in FMA score were a result of neurological compensation.

The iSNR is a measure for the integrity of the sensory pathways. Increased integrity of the sensory pathways related to true motor recovery could be considered as neurological restitution; the previously damaged sensory pathways are restored. Though, if this was the case, this increase in integrity of the sensory pathways related to FMA score should also have been found during the relax and force task, as they were measured at the same time in the same patients. However, the iSNR was not found to be related to FMA score during the relax and force tasks. Since the relation between iSNR and FMA score during the position task is thought to be a result of the amount of co-contraction strategy, it is not clear whether this can be considered as true neurological recovery.

4.6 Limitations

The promising results of this study should be considered in the context of the following limitations. EEG is known to be a very noisy imaging technique. Besides the cortical activity which is measured with EEG, also line noise, eye blinks and activity from the eye muscles and other facial muscles are detected with EEG [35]. Most of the noise was eliminated during the analyses, however there is apparently still noise left in the final data set as can be seen in the topographical plots in the appendices. Most of the patients show increases in SNR at locations in the brain where it is not expected (see the SNR topographical plots, uneven numbered Figures 9-33). For example, the SNR topographical plot of patient 1 (Figure 9) during the relax task of the first measurement also shows, besides the increase in SNR in the sensorimotor cortex, an increase in the SNR around the right ear which is probably the result of muscle activity. Even though the EEG data is very noisy, in almost all measurements the electrode with the highest SNR is placed above the sensorimotor cortex. The channel plots in the appendices (even numbered Figures 10-34) show the iSNR and the 'percentage of maximum' for all three tasks in the upper right corner (as can be read in Appendix E). In almost all measurements of all patients, this percentage is 100%, meaning that the electrode selected to calculate the iSNR (SNR_{ROI}) is also the electrode with the highest SNR. This indicates that the noise hardly influenced the calculation of the iSNR. Also, when averaging the SNR topographical plots, the noise is canceled out as can be seen in Figure 3.

Comparing the iSNR between tasks and measurements was done with two different tests, a factorial repeated measures ANOVA and a linear mixed model analysis. Due to missing data for some of the patients (e.g. not all 13 patients completed all three tasks four times), the choice for executing a factorial repeated measures ANOVA was not exquisite. The executed factorial repeated measures ANOVA deletes subjects list-wise when data is missing [36], which resulted in the test to be executed over data of only 8 patients. This also explains the differences in mean iSNR values reported for the two tests (see Section 3.3). The most correct statistical analysis would be a linear mixed model analysis because of its ability to work with missing data [36]. However, since this study was a first exploration of the data, the choices made in this complex analysis may not be divine. Therefore, both tests were conducted. As both tests gave the same results, the conclusions drawn from these results are assumed to be reliable.

The patients included in this study are a selection of the participants of the 4D EEG project. For this project, as much stroke patients as possible were asked to participate. Therefore, the study sample of this study depends on coincidence and no influence could be exerted on it. However, this may have caused some limitations in the study sample. Firstly, as can be seen in Table 1, the study sample of this study is skew; only one female participated in this study. Functional recovery is shown to be lower in female stroke patients compared to male stroke patients, despite adjustments for comorbidities and age [50,51]. The improvements in FMA score in this study would therefore have been smaller if there were as much female as male patients included. The results in this study thus apply to the male stroke population, but it is uncertain if it applies to the female stroke population as well. Secondly, only 13 of the 49 patients that participated in the 4D EEG project completed enough measurements to be included into this study (see Figure 6 in appendix 7.1). Apparently the position and/or force task are too difficult to complete for most of the patients. This is in line with how often the

tasks were completed during the 4D EEG project. The relax task was completed 80% of the time, the force task 50% and the position task only 40% (see Figure 6). Additionally, the 13 patients that were included into the study had significantly higher FMA scores on all the four measurements (52.1±4.5) than the patients that were not included (34.8±24.5) (a factorial repeated measures ANOVA showed a significant main effect of inclusion with $F(1,31)=6.92$, $p=0.01$), as can be seen in Figure 8. The study sample therefore mainly represents the patients that have better recovery patterns.

The most important limitation of this study is that the promising results with regard to the relation between the iSNR and FMA score are found in the position task. As described previously, the position task was completed least often. Also, the patients that were not included in this study, had worse motor function than the patients that were included. Therefore the position task is thought to be the most difficult task for stroke patients and especially for patients with worse recovery patterns. However, the focus in research about stroke recovery should lie on those patients. Part of the stroke patients with initial poor prognosis of recovery of motor function do still recover after six months [52]. The brain activity during motor recovery of these cross-over patients are most interesting to study in the context of developing neurological biomarkers, because they show the biggest improvements in motor function. Addtionally, they may have the greatest benefit of therapies during the sub-acute stroke phase [27]. In figure 8 can be seen that there are only some cross-over patients in the 4D EEG project, of which only two were included in this study (patients 3 and 4).

4.7 Recommendations

Before the iSNR could be implemented as EEG biomarker for motor recovery after stroke in the clinical setting in the future, a lot more research should be done. There are several recommendations for future research. Firstly, with regard to the limitation described above, future research could restrict the study protocol to the relax and position task only. By eliminating the force task, patients will get less fatigued during the measurements. Also, more time will be available to perform more repetitions of the position task. Thereby, more patients, namely the patients with worse recovery patterns, will potentially be able to complete the position task more often. This would result in a bigger sample size. Secondly, future research should evaluate the relation between baseline iSNR and FMA score during and at the end of the recovery process. This way, the predictive ability of the iSNR could be assessed.

5 Conclusion

- The iSNR during the position task is potentially a EEG biomarker for upper limb motor recovery after stroke as indicated by the found moderate relation between the iSNR and FMA score in sub-acute stroke patients.
- The iSNR during the position task is lower as compared to the iSNR during the relax and force tasks, potentially resulting from the underlying neurological strategies in the execution of the different control tasks.
- The found relation between the iSNR and FMA score suggests that the integrity of the sensory pathways plays a role in motor recovery after stroke.

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Appendices

A Completed tasks and measurements 4D EEG project

Figure 6 represents a table with the completed tasks and measurements for all the 49 patients that participated in the 4D EEG project.

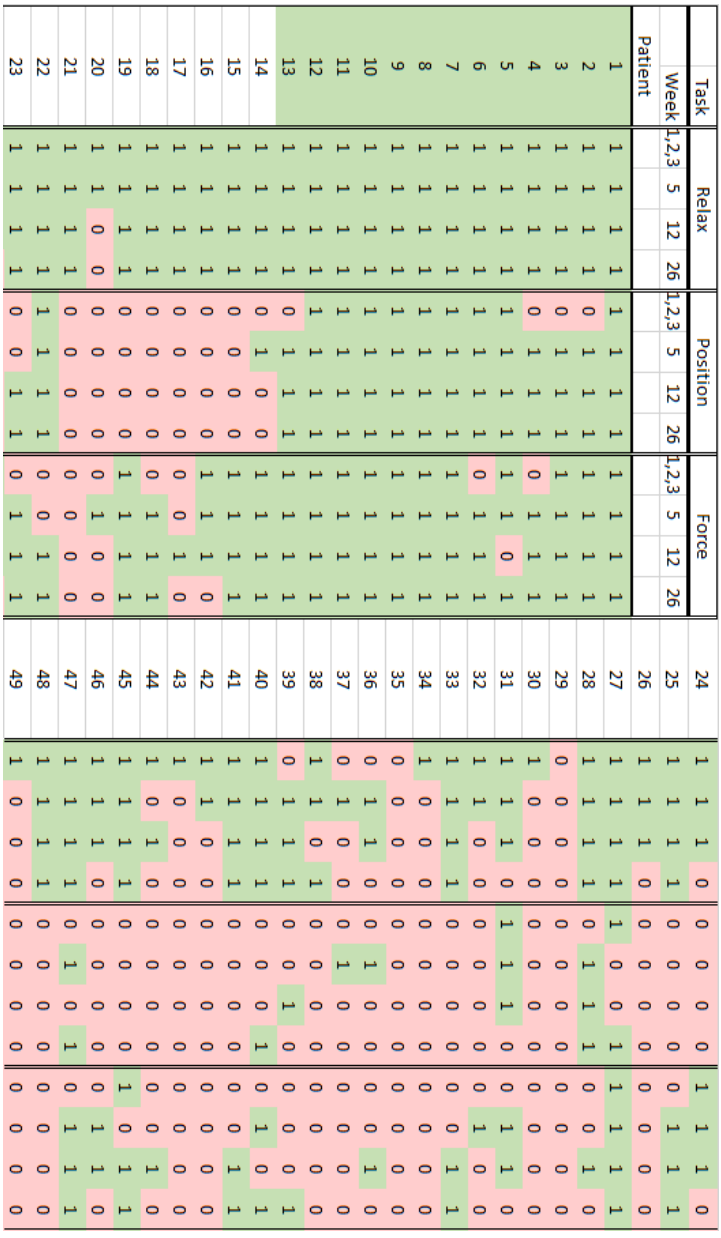


Figure 6: Completed tasks and measurements for all 49 patients of the 4D EEG project sorted by inclusion date. Completed measurements are indicated by a green '1' and missing measurements are indicated by a red '0'. The 13 patients included in this study are marked in green.

B EmNSA data

Figure 7 represents a table with the scores on the EmNSA for all 13 patients and the corresponding sensory impairment group.

Test	Light Touch				Pressure				Pin prick			
Week	1,2,3	5	12	26	1,2,3	5	12	26	1,2,3	5	12	26
Patient												
1	8	8	8	8	8	8	8	8	8	8	8	8
2	8	8	8	8	8	8	8	8	8	8	8	8
3	7	7	8	8	8	8	8	8	8	8	8	8
4	8	8	8	8	8	8	8	8	8	8	8	8
5	3	6	5	7	6	8	8	8	7	8	7	8
6	0	3	7	7	1	8	8	8	2	8	8	8
7	8	8	8	8	8	8	8	8	8	8	8	8
8	8	8	8	8	8	8	8	8	8	8	8	8
9	8	8	8	8	8	8	8	8	8	8	8	8
10	6	8	8	8	8	8	8	8	8	8	8	8
11	8	8	8	8	8	8	8	8	8	8	8	8
12	8	8	8	8	8	8	8	8	8	8	8	8
13	8	8	8	8	8	8	8	8	8	8	8	8
	Discrimination				Propriocepsis				Sensory impairment			
	1,2,3	5	12	26	1,2,3	5	12	26	1,2,3	5	12	26
1	8	8	8	8	8	8	8	8	n	n	n	n
2	8	8	8	8	8	8	8	8	n	n	n	n
3	6	6	7	7	8	8	8	8	m	m	m	m
4	8	8	8	8	8	8	8	8	n	n	n	n
5	6	6	5	7	7	8	8	8	s	m	s	m
6	0	6	8	7	3	8	8	8	s	m	m	m
7	8	8	8	8	8	8	8	8	n	n	n	n
8	8	8	8	8	8	8	8	8	n	n	n	n
9	8	8	8	8	8	8	8	8	n	n	n	n
10	5	8	6	8	8	8	8	8	m	n	m	n
11	8	8	8	8	8	8	8	8	n	n	n	n
12	8	8	8	8	8	8	8	8	n	n	n	n
13	4	7	8	7	8	8	8	8	m	m	n	m

Figure 7: Scores on the 5 sub-tests of the EmNSA during the four measurements. Full scores are marked in green. The sensory impairment group (s=severe, m=mild and n=none) which the patients would be assigned to according to [21].

C FMA score over time 4D EEG project

Figure 8 shows the FMA scores over time after stroke for all the 49 patients that participated in the 4D EEG project

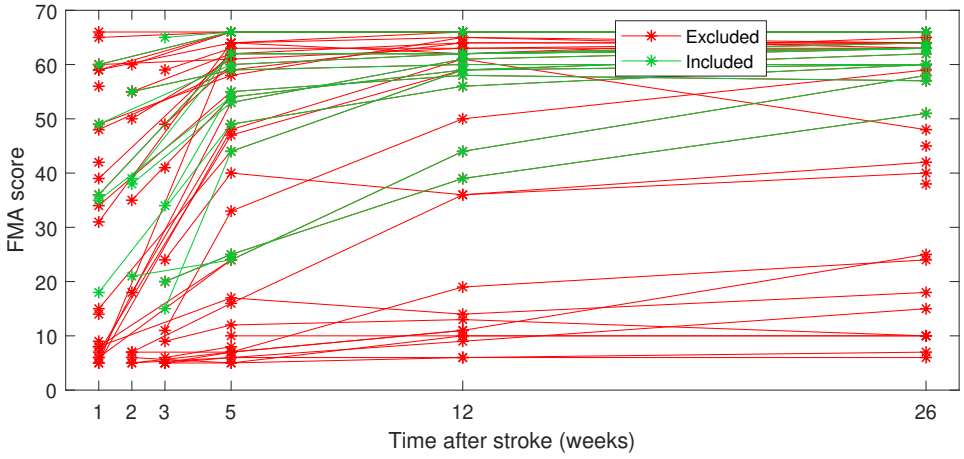


Figure 8: FMA score plotted against time after stroke for all patients of the 4D EEG project (n=49). Included patients are marked in green and excluded patients are marked in red.

D Channel and epoch removal algorithm

It can happen that data contains much noise, for example due to a high impedance of the EEG electrode. An algorithm was created in MATLAB 9.5 (The Mathworks, Inc., Natick, Massachusetts, United States) to select EEG channels and epochs that contain too much noise and that will influence the results. The algorithm makes use of the method of finding extreme values in potential by means of standard thresholding. This method of detecting artifacts was chosen considering both performance and speed of computation [53]. The algorithm uses the EEG lab function *pop_eegthresh*, which detects where the EEG signal exceeds a certain threshold. One data file contains data of one patient for one measurement of one task. The data file consists of EEG signal of 64 channels x 160 epochs. First, for all epochs of all channels, the algorithm detects if the signal exceeds the predefined threshold band of -90 to 90 mV. If the threshold is exceeded, that epoch of that channels is marked with an '1', if not, it is marked with a '0'. This results in a matrix of 64 x 160, containing ones and zeros. Next, the algorithm marks the channels in which more than 55% of the epochs where marked with an '1'. These are the channels that will be removed, because they contain too much noise in most of the epochs. For the rejection of epochs, something similar was done. The EEG lab function *pop_eegthresh* was executed again with a threshold band of -80 to 80 mV, but now only for the channels that were kept. The algorithm then detects the epochs for which more than 5 channels were marked with an '1'. Those epochs will be removed from the data. As a result, after removing those marked channels and epochs, the EEG data will be free of most of the excessive noise.

E SNR topographical and channel plots

In this appendix, the SNR data is plotted for each patient. This makes it possible to go into more detail when discussing the data. On pages 27-52, the SNR topographical plots and channel plots are shown for all 13 patients. To prevent unnecessary repetition of information, the captions of the figures 9-34 are presented below.

All the figures with uneven numbers show for one patient the SNR topographical plots averaged over all trials for the three tasks and four measurements.

All the figures with even numbers show for one patient the averaged SNR over all trials plotted against channel label for each task, based on descending order of SNR during the relax task. Figures (a) show measurement 1, figures (b) measurement 2, figures (c) measurement 3 and figures (d) measurement 4. The squared markers indicate the nine electrodes in de ROI. In the upper left corner, the iSNR and the percentage of maximum is shown for each task. The percentage of maximum is the percentage of the SNR_{ROI} of the highest SNR of all electrodes, providing information about if the electrode with the highest SNR belonged to the ROI.

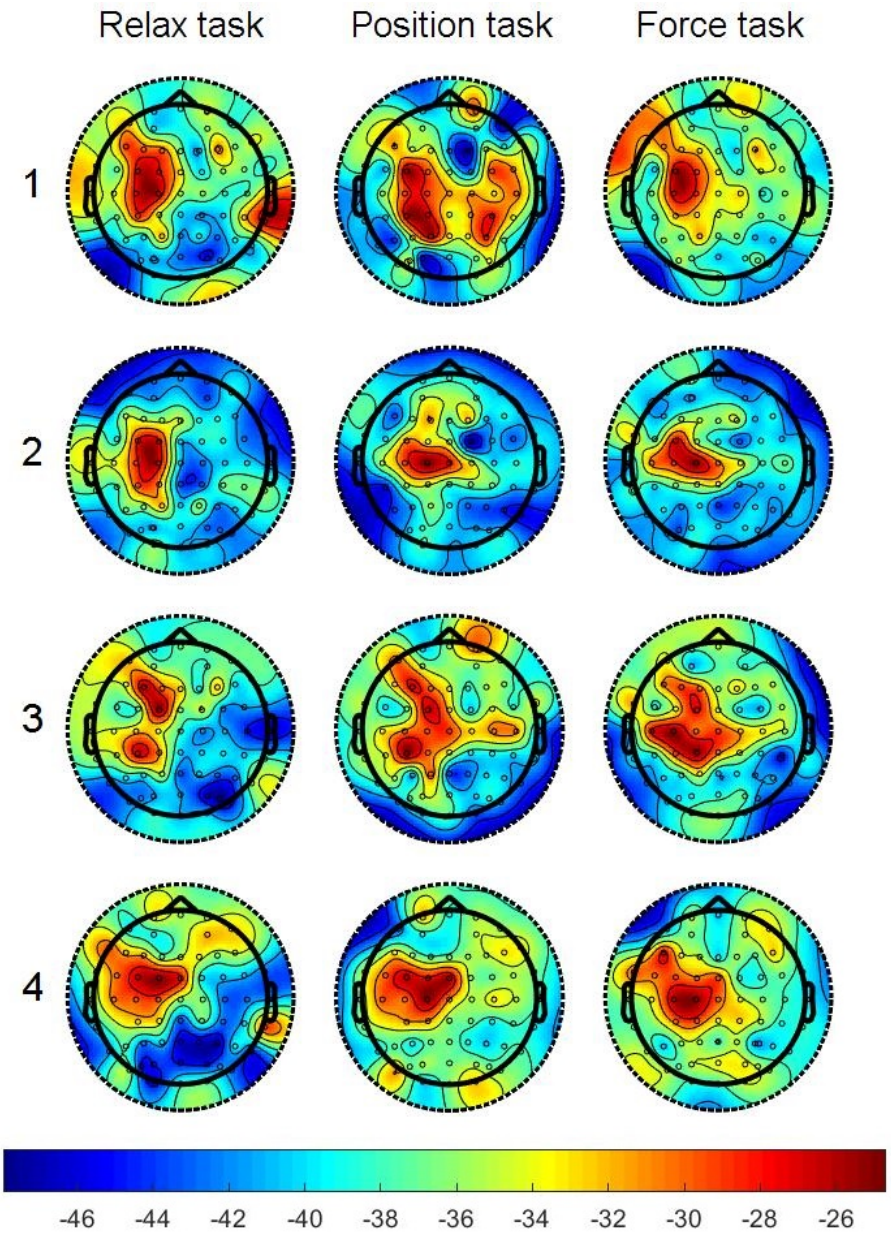
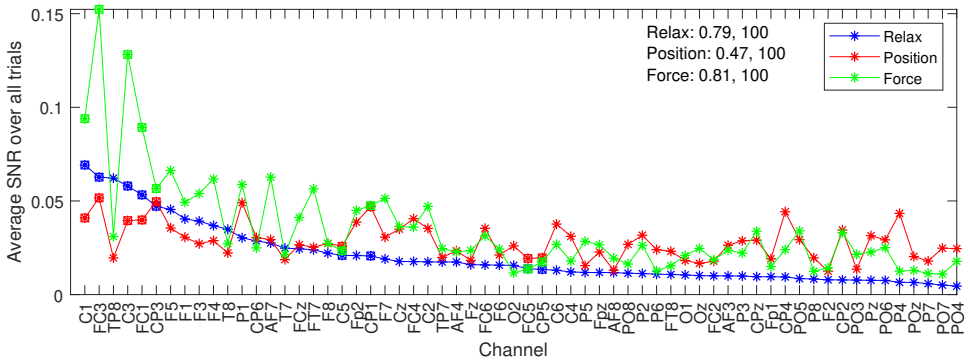
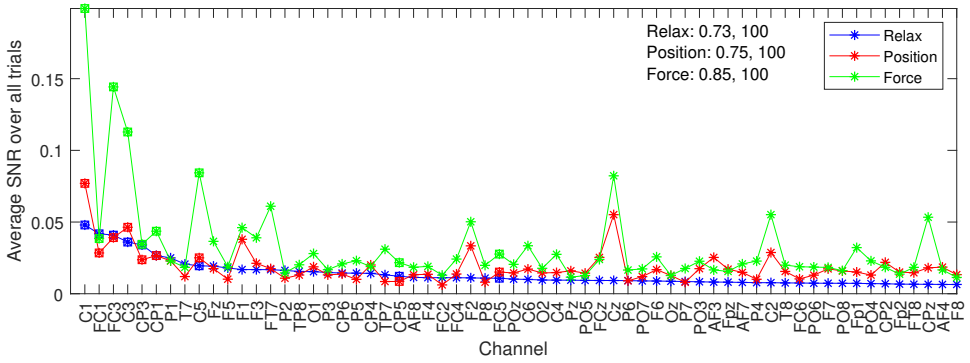


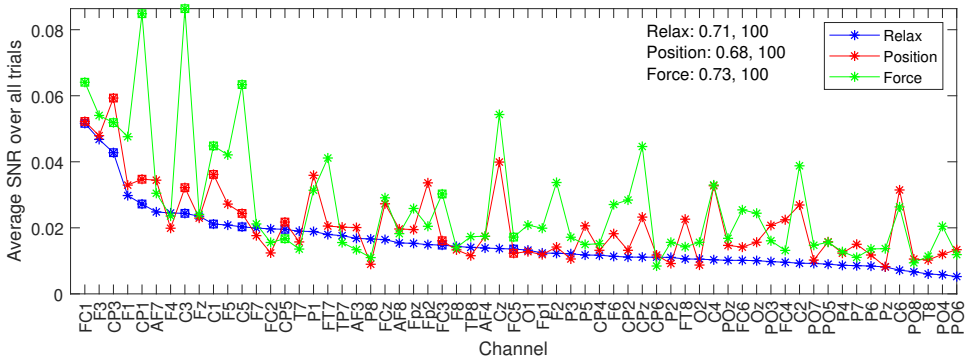
Figure 9: SNR topographical plots of patient 1.



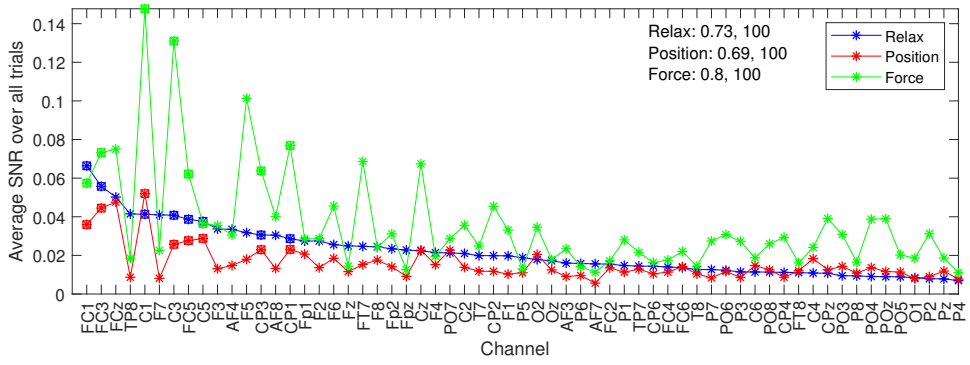
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 10: SNR plotted against channel label for patient 1.

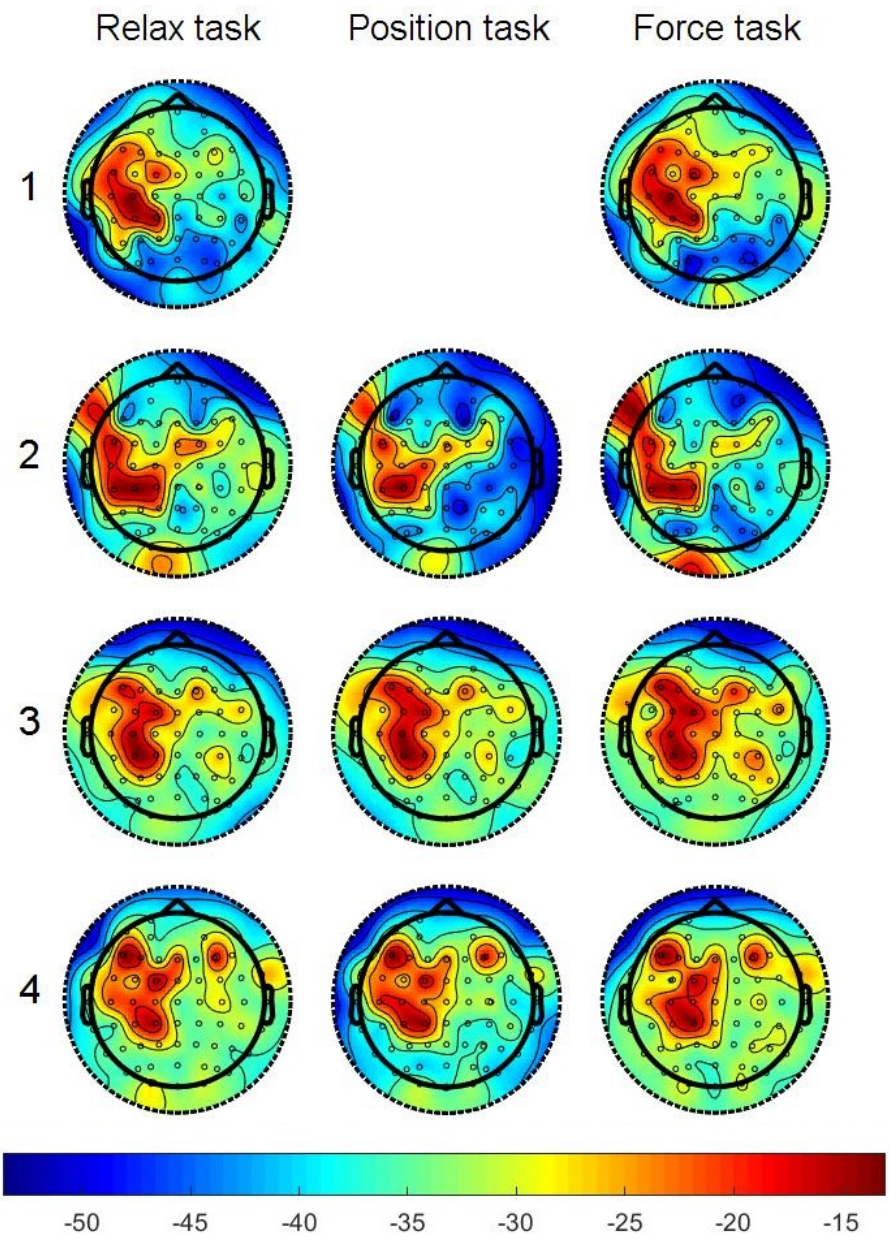
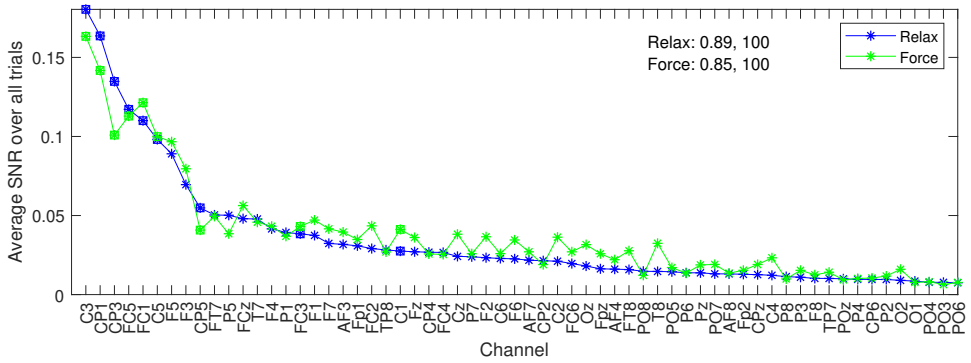
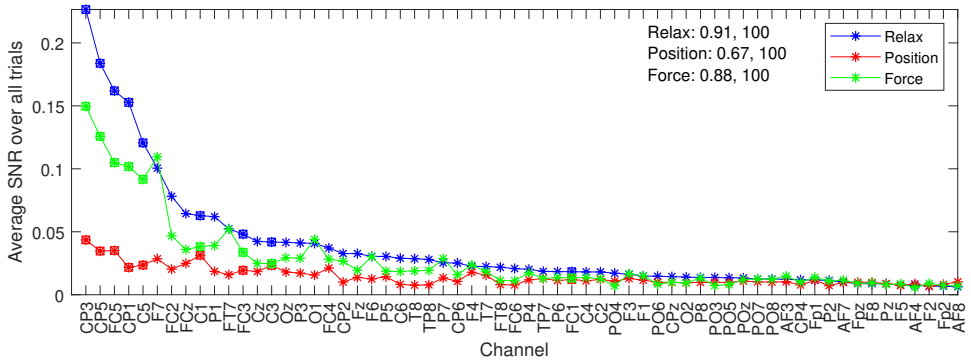


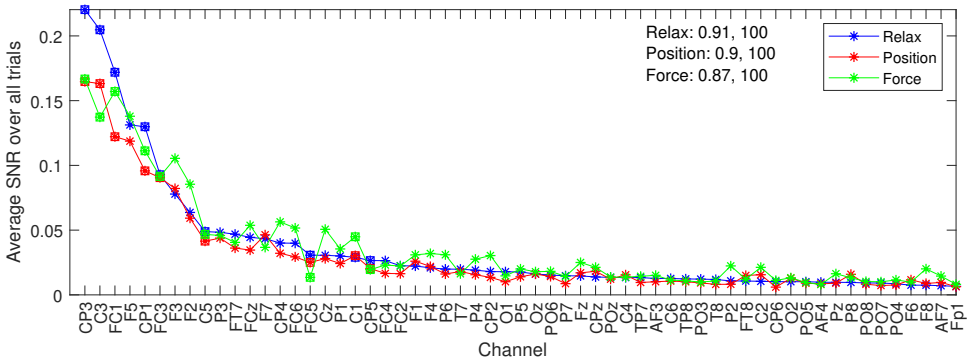
Figure 11: SNR topographical plots of patient 2.



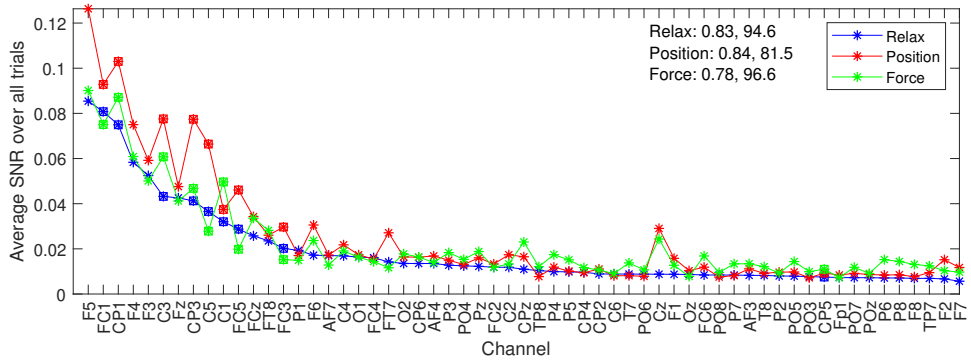
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 12: SNR plotted against channel label for patient 2.

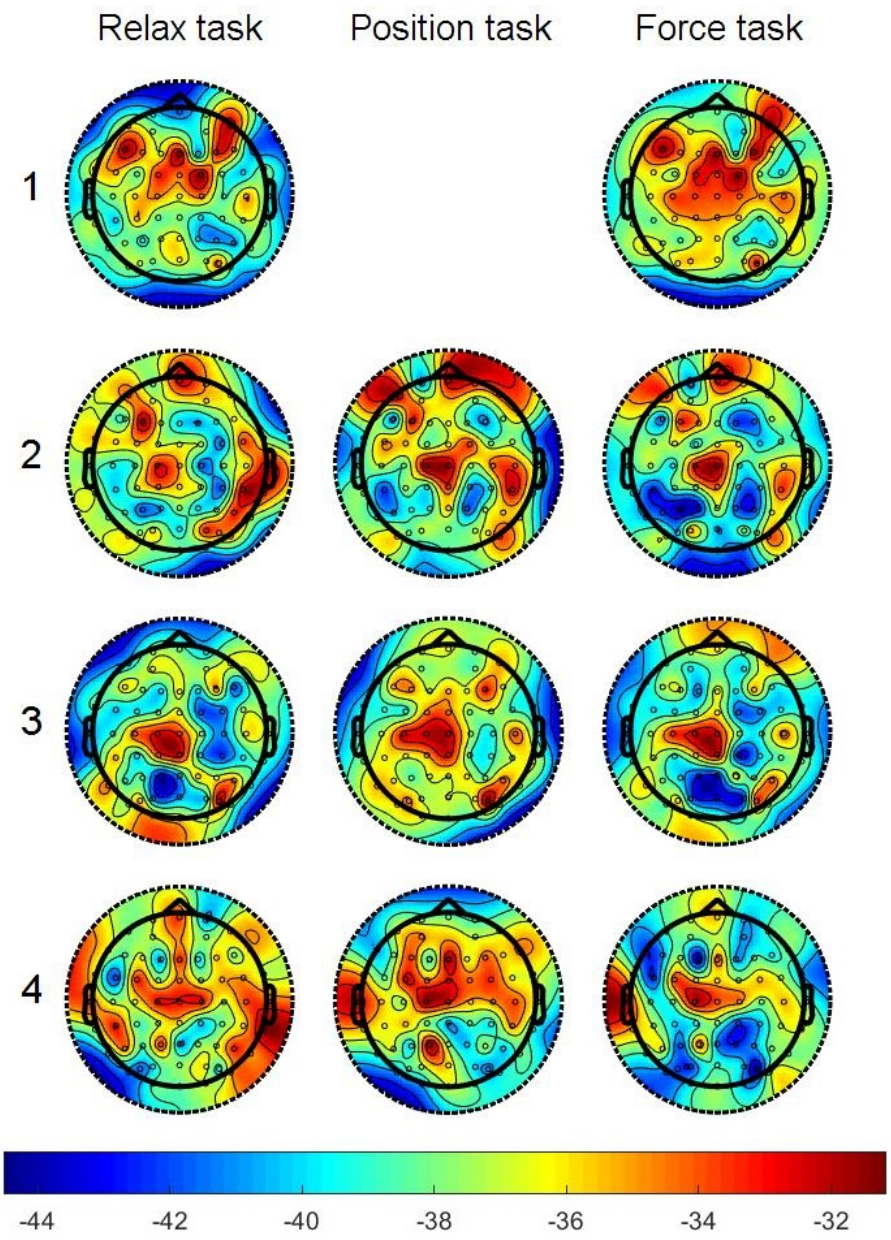
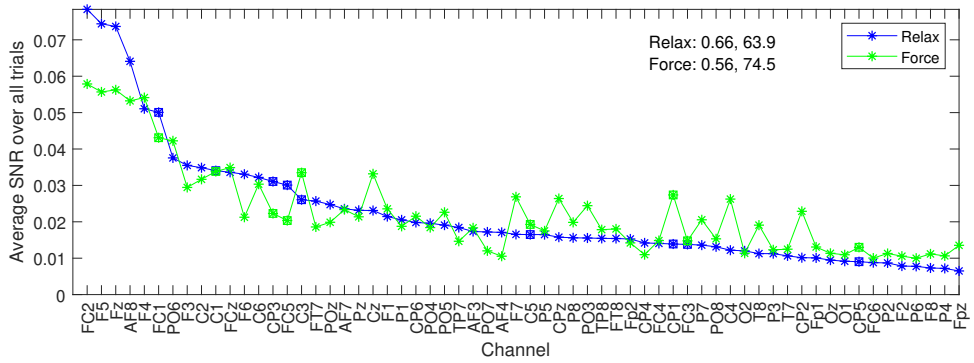
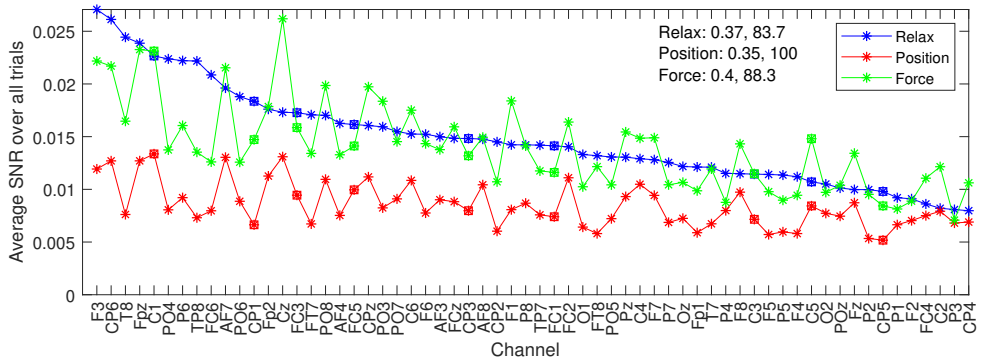


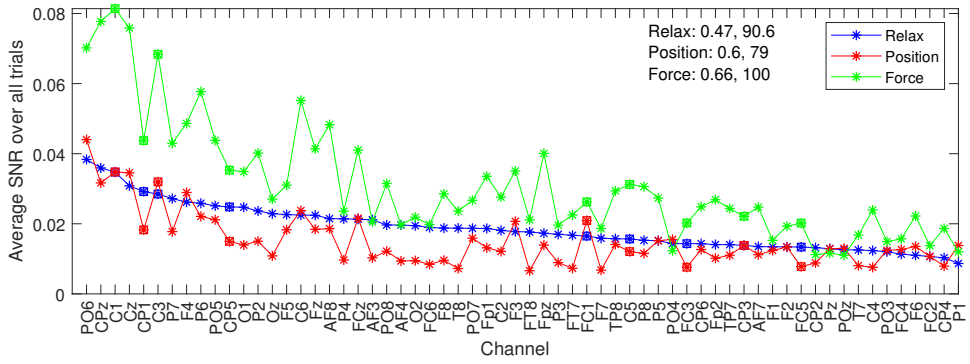
Figure 13: SNR topographical plots of patient 3.



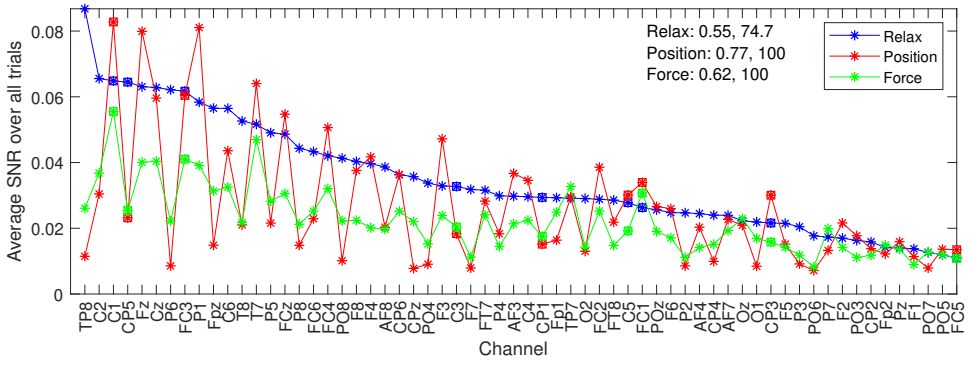
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 14: SNR plotted against channel label for patient 3.

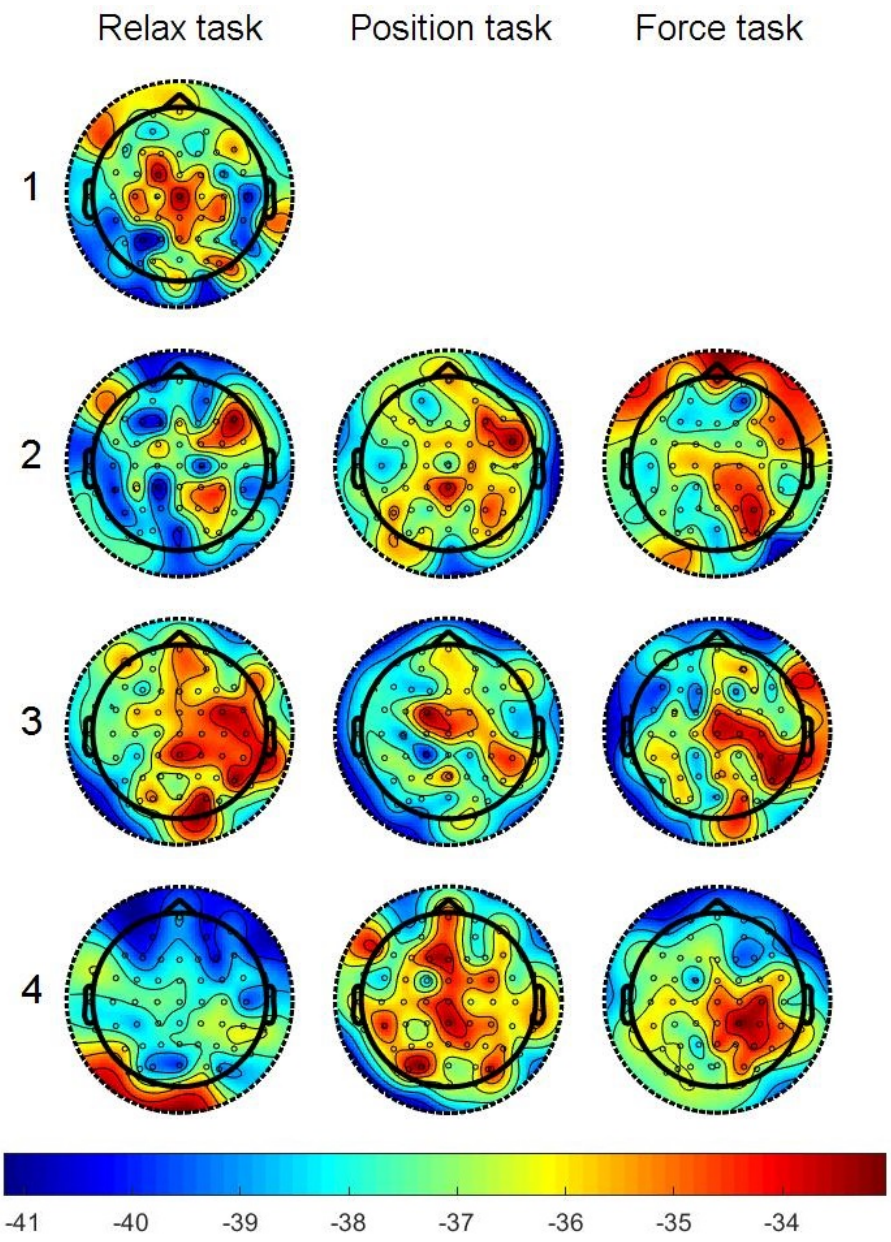
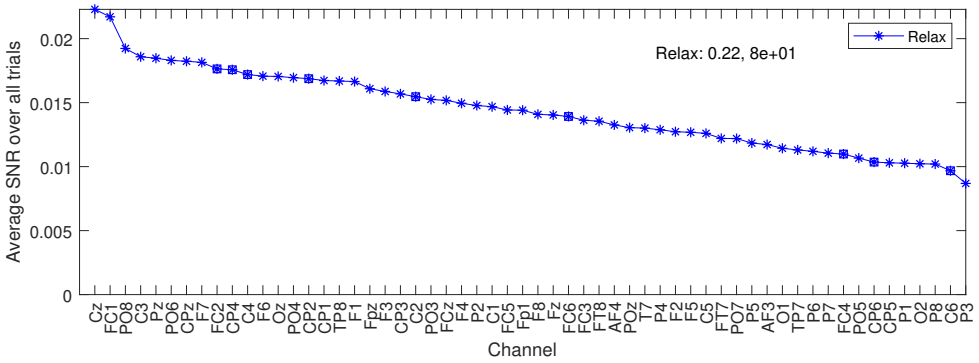
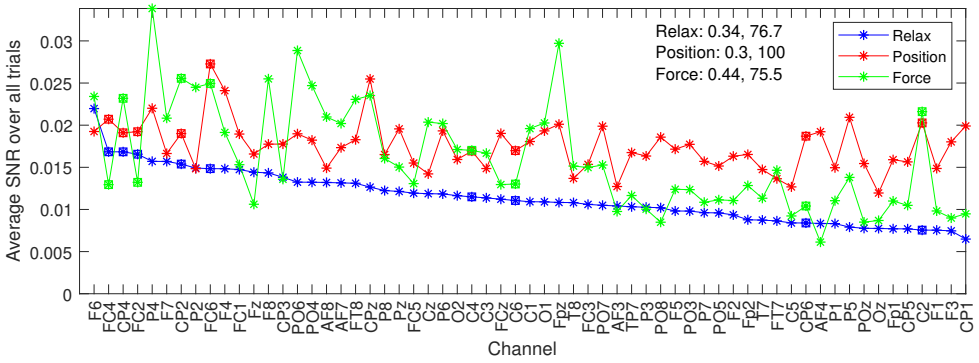


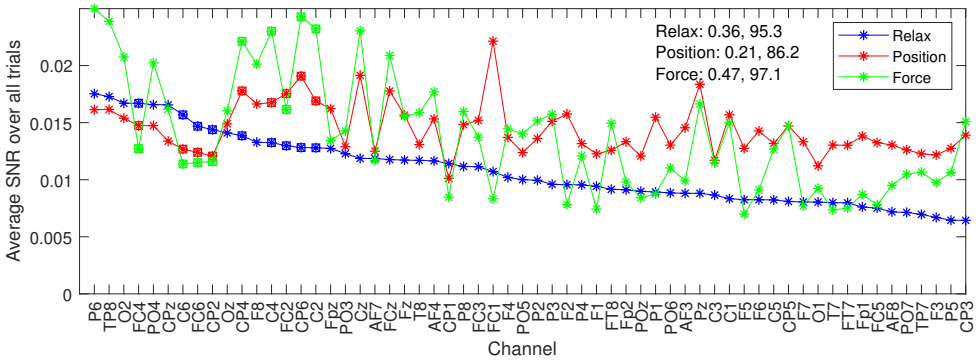
Figure 15: SNR topographical plots of patient 4.



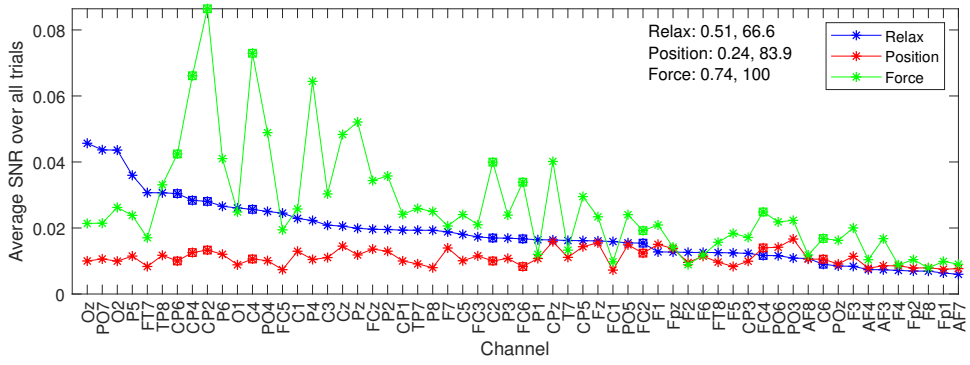
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 16: SNR plotted against channel label for patient 4.

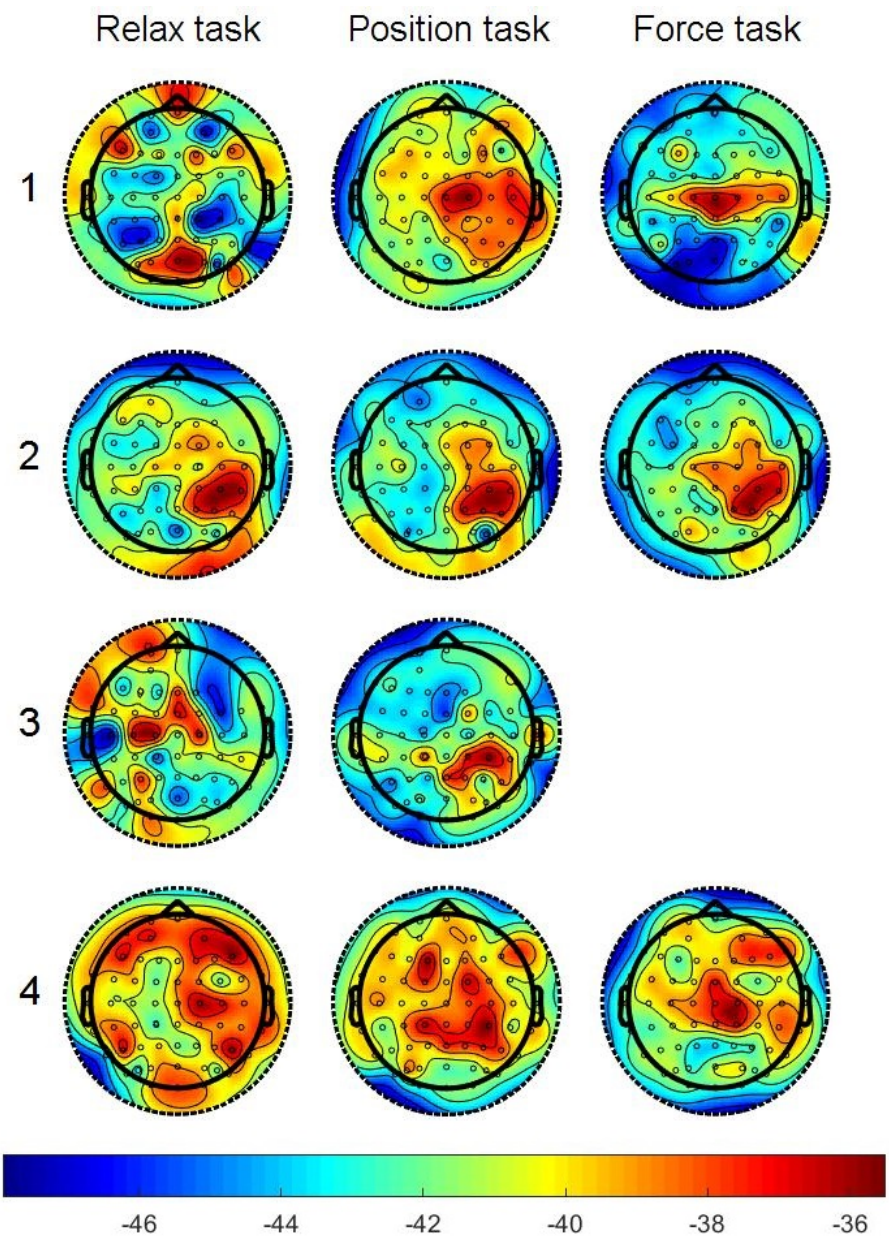
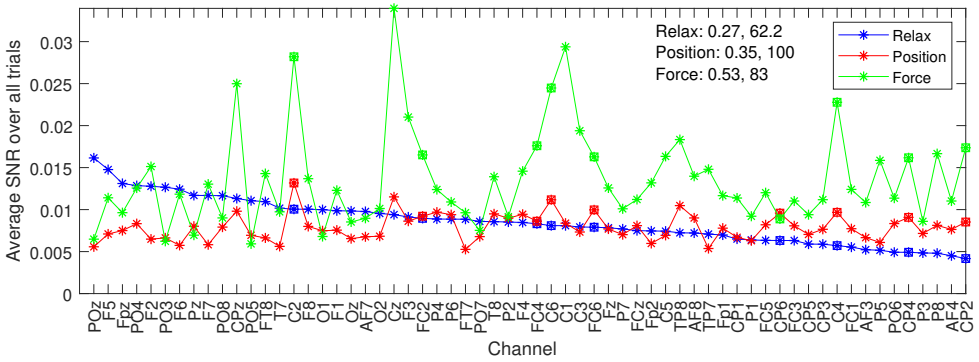
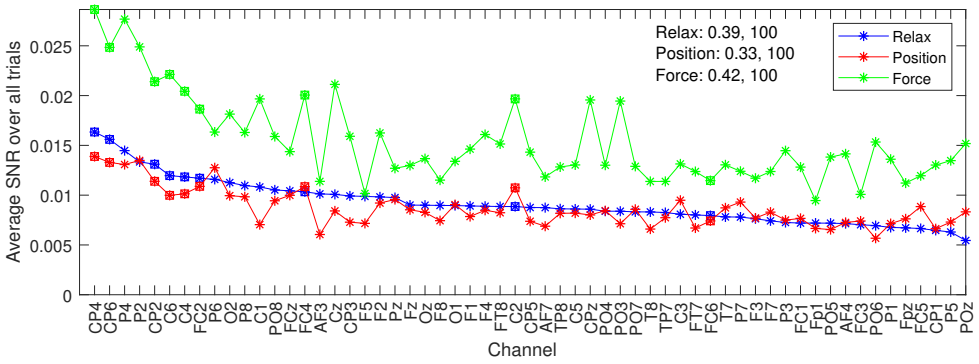


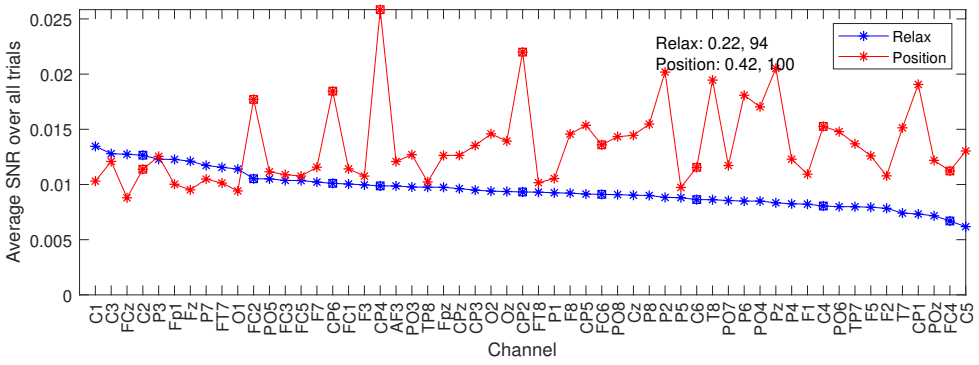
Figure 17: SNR topographical plots of patient 5.



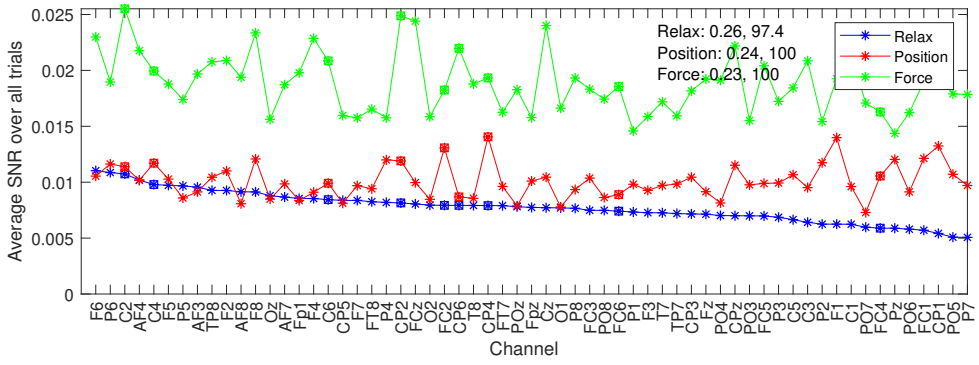
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 18: SNR plotted against channel label for patient 5.

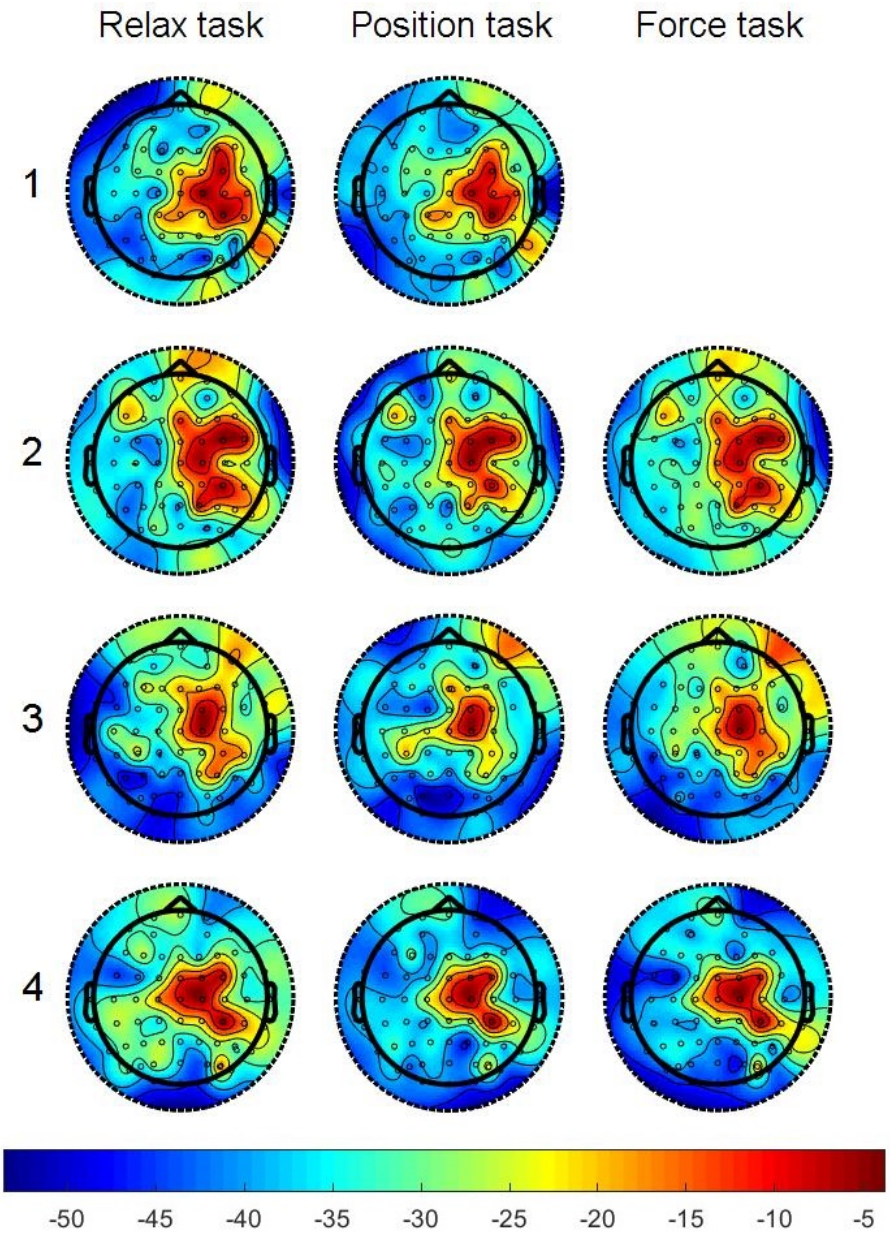
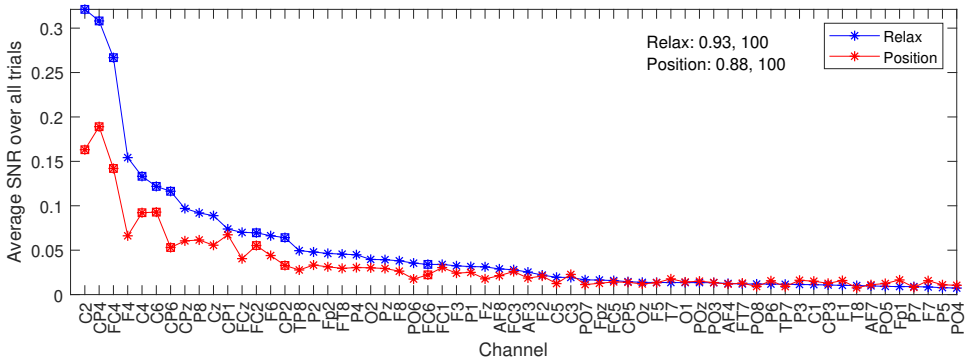
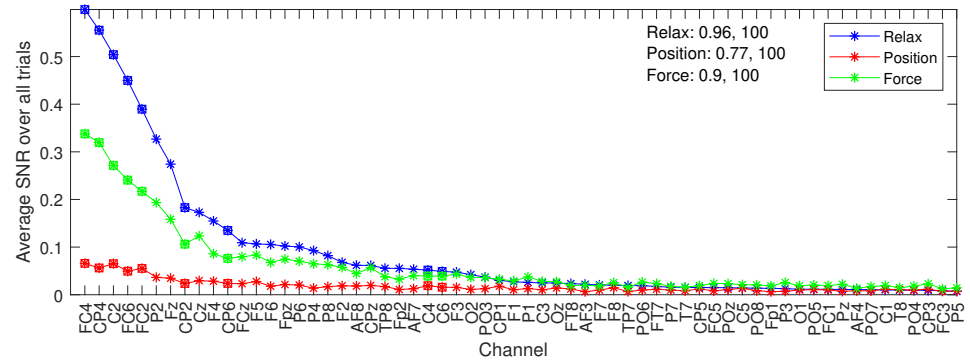


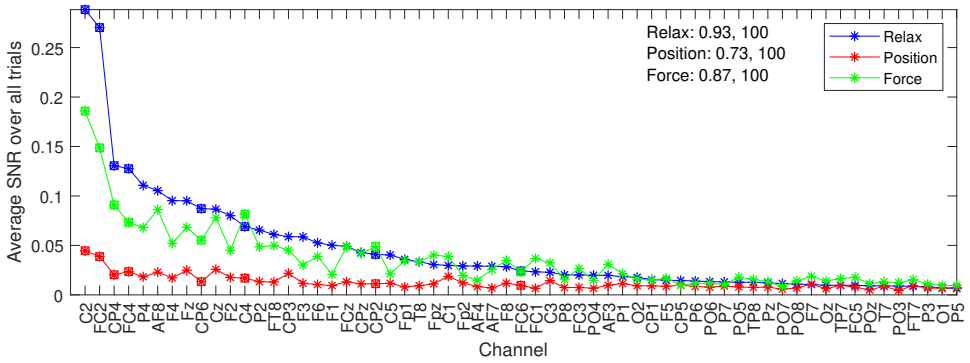
Figure 19: SNR topographical plots of patient 6.



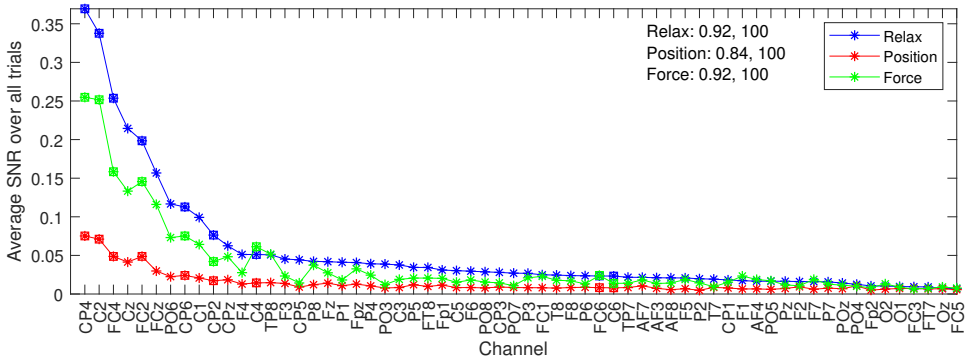
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 20: SNR plotted against channel label for patient 6.

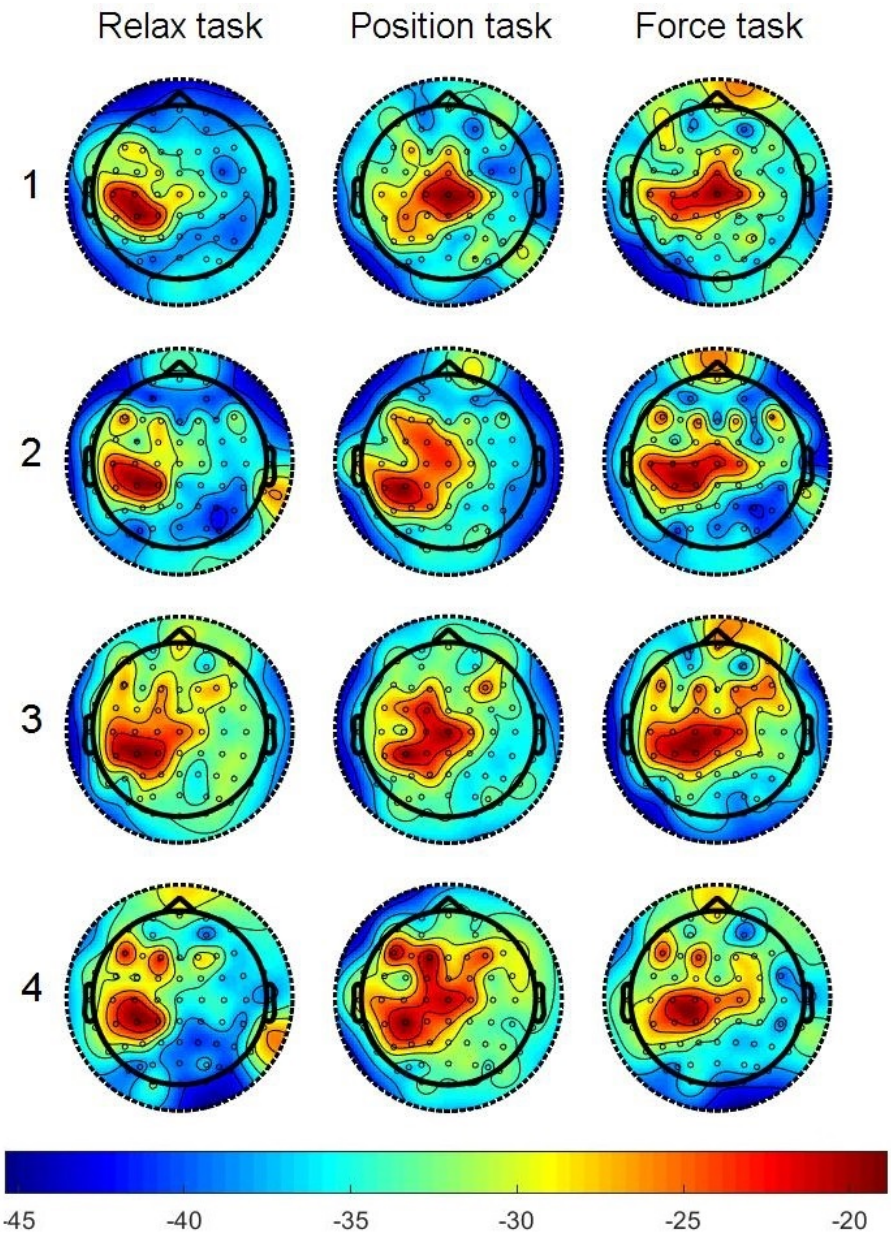
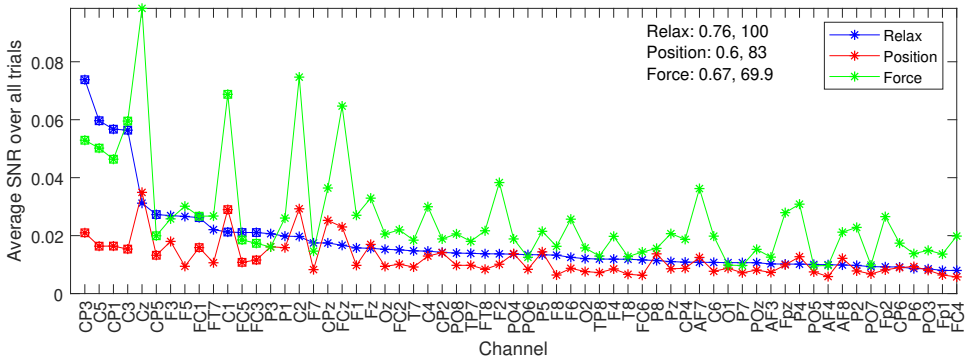
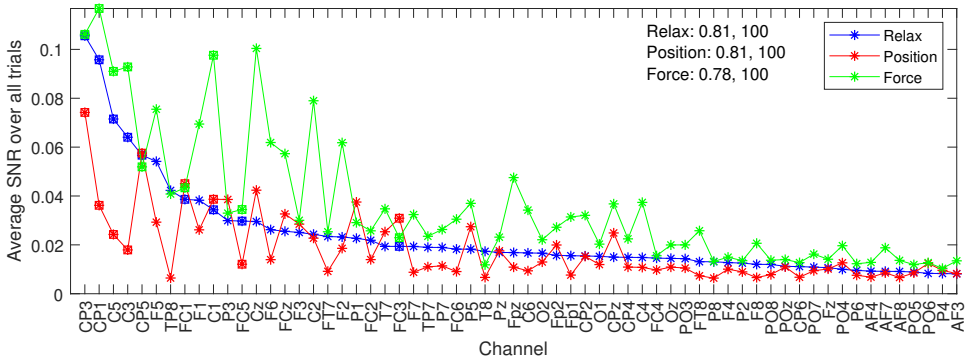


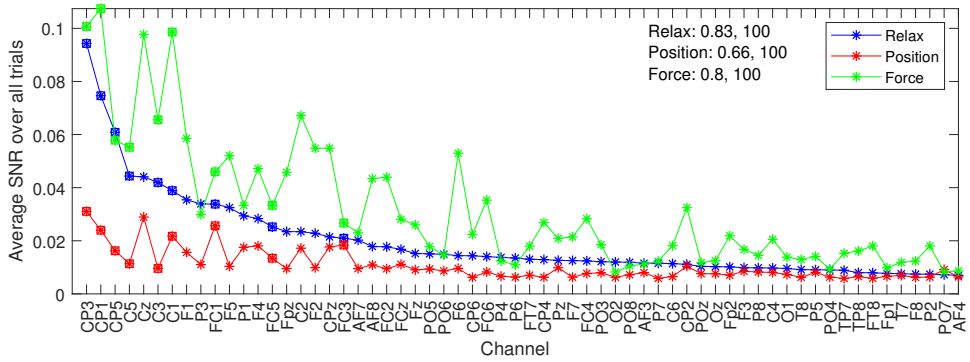
Figure 21: SNR topographical plots of patient 7.



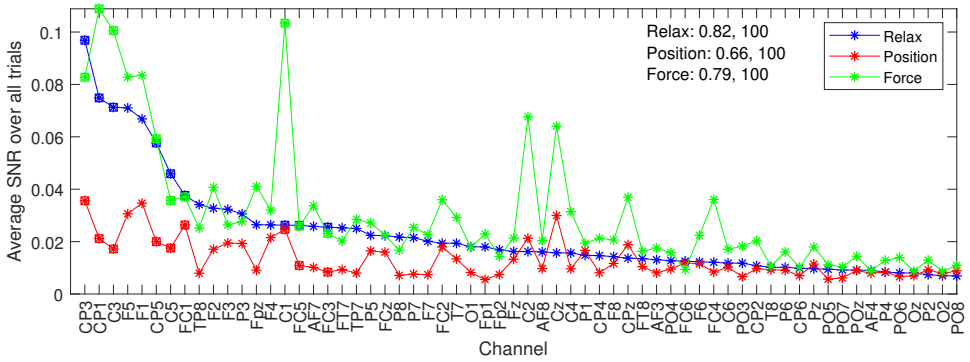
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 22: SNR plotted against channel label for patient 7.

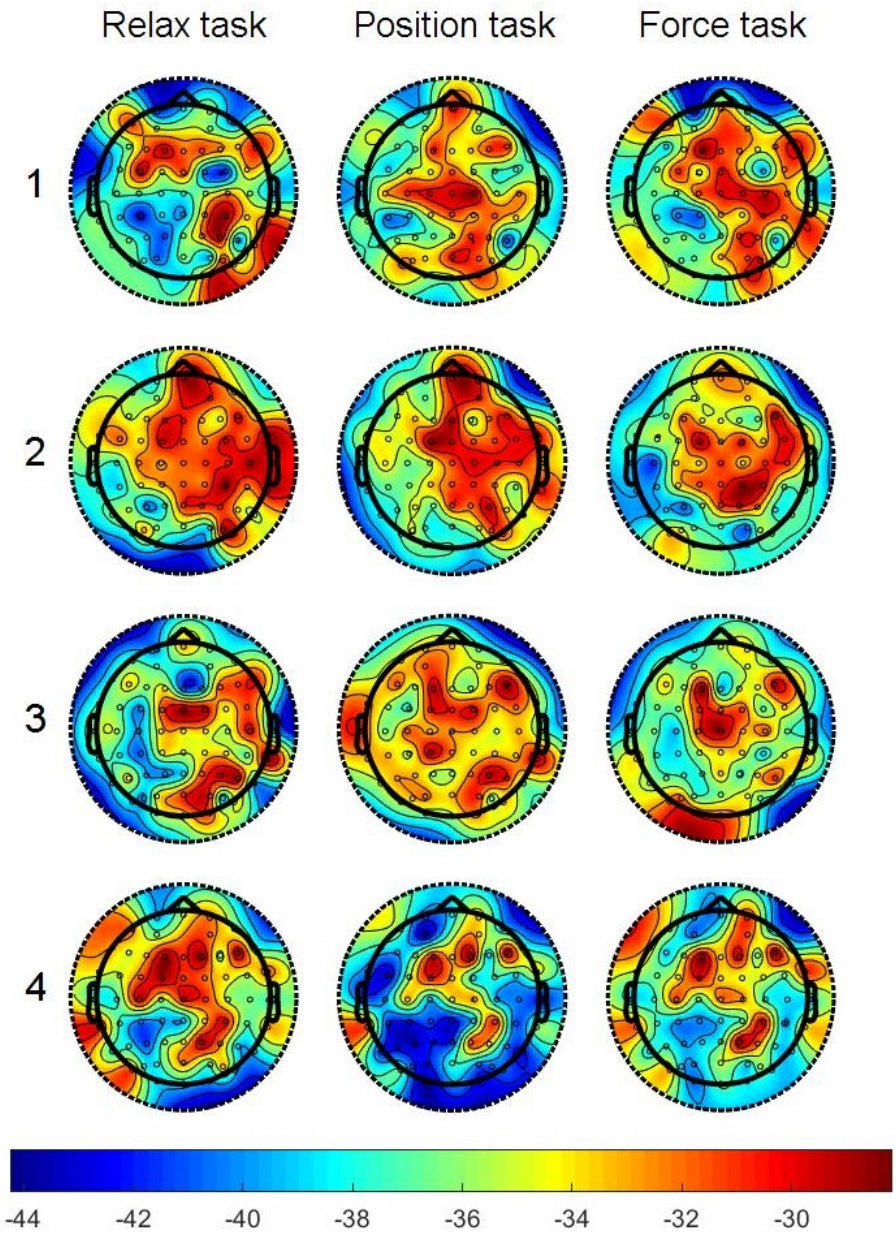
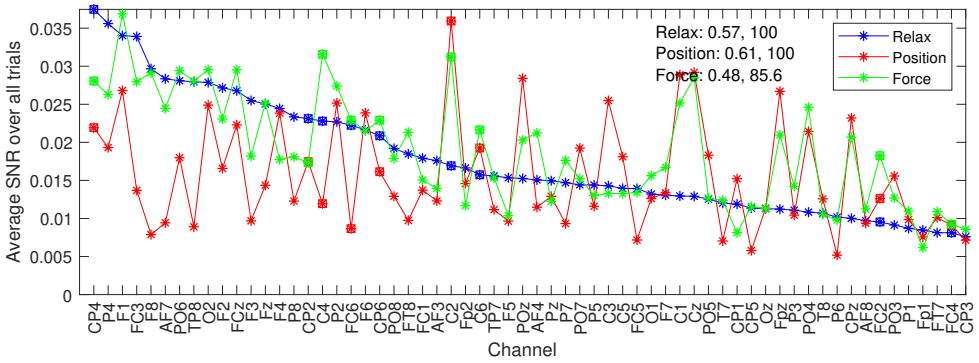
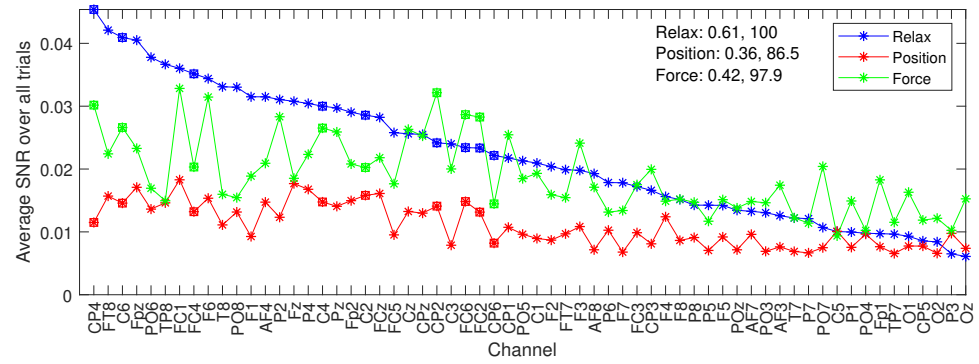


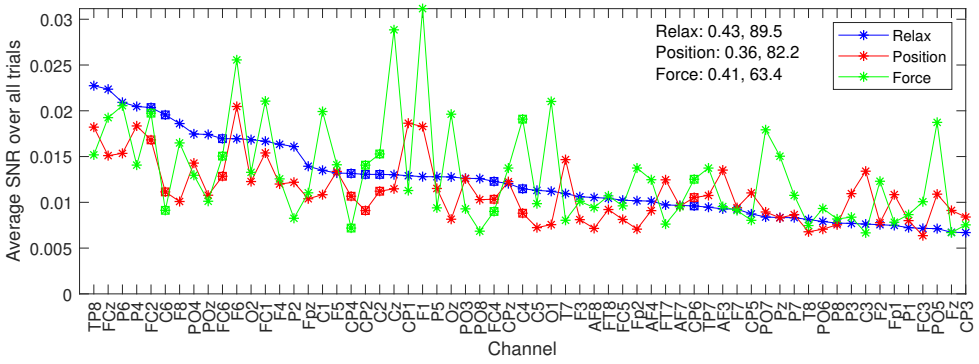
Figure 23: SNR topographical plots of patient 8.



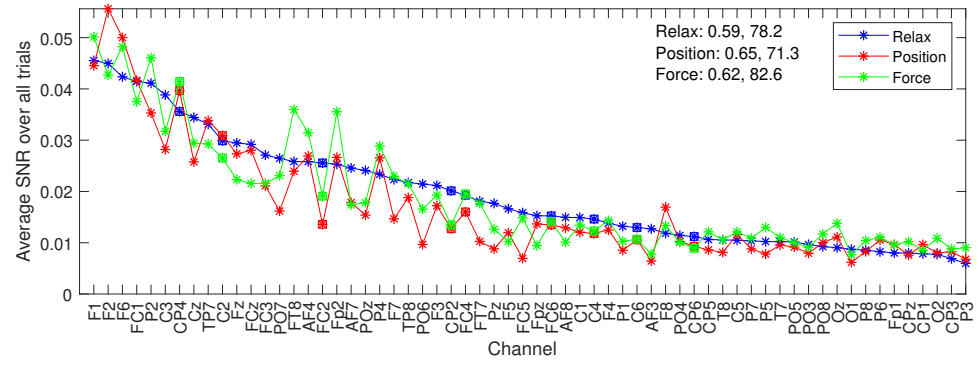
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 24: SNR plotted against channel label for patient 8.

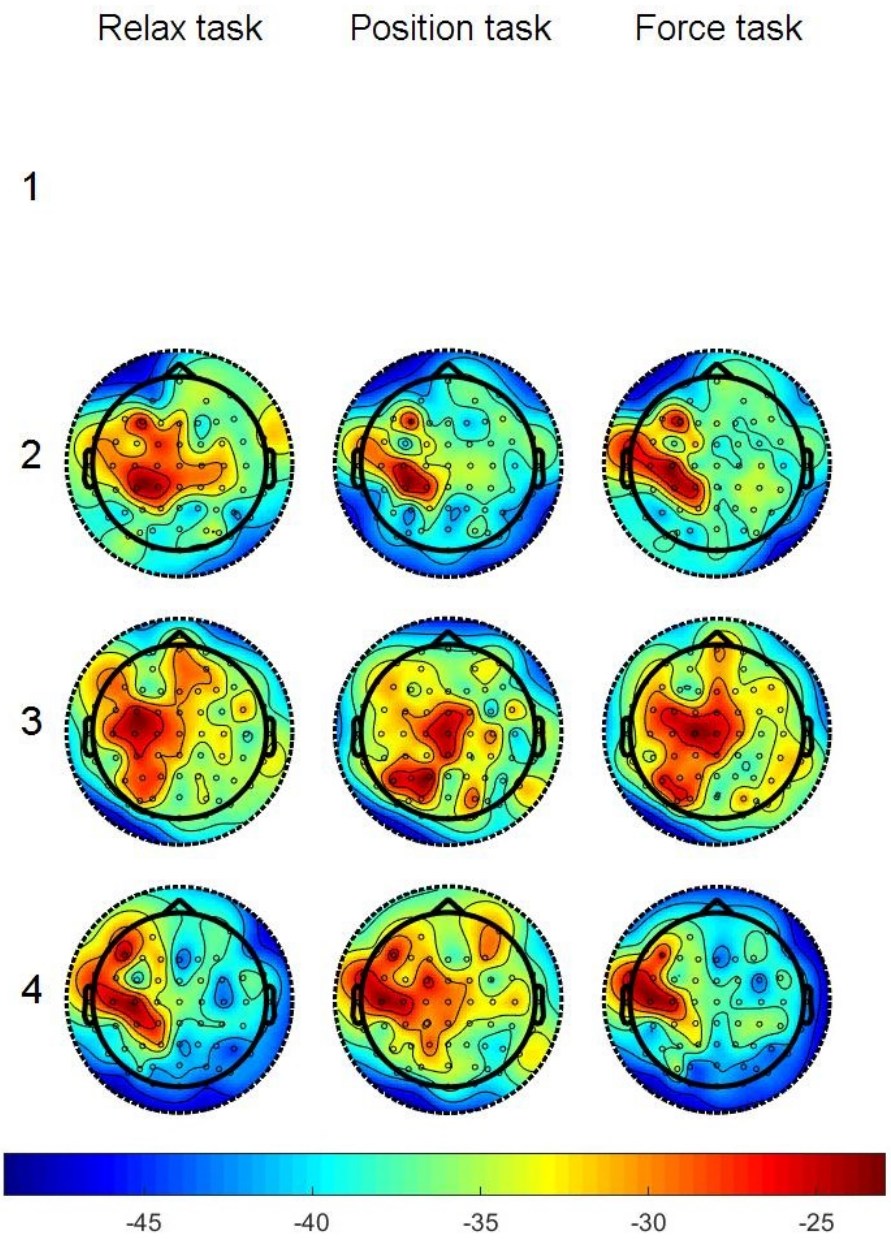
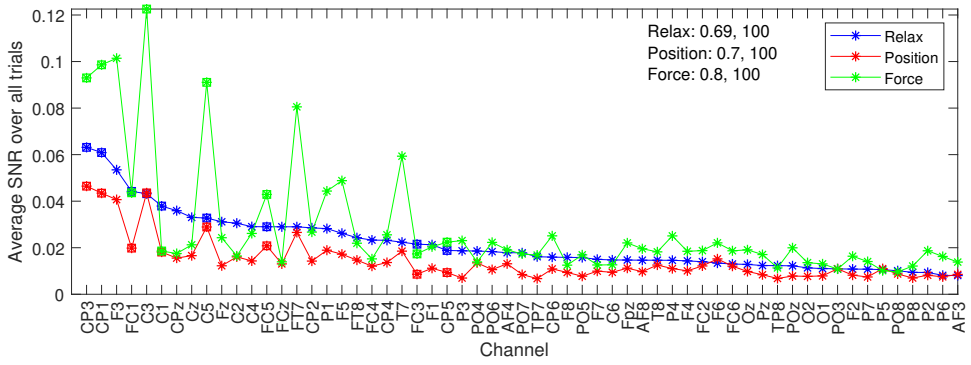
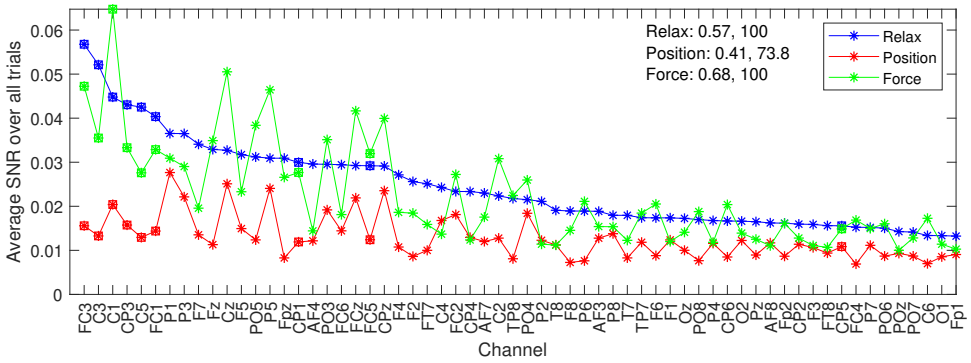


Figure 25: SNR topographical plots of patient 9.

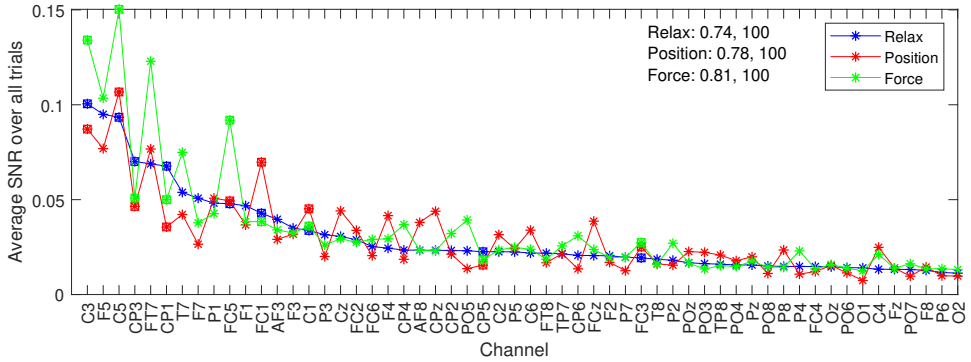
(a)



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 26: SNR plotted against channel label for patient 9.

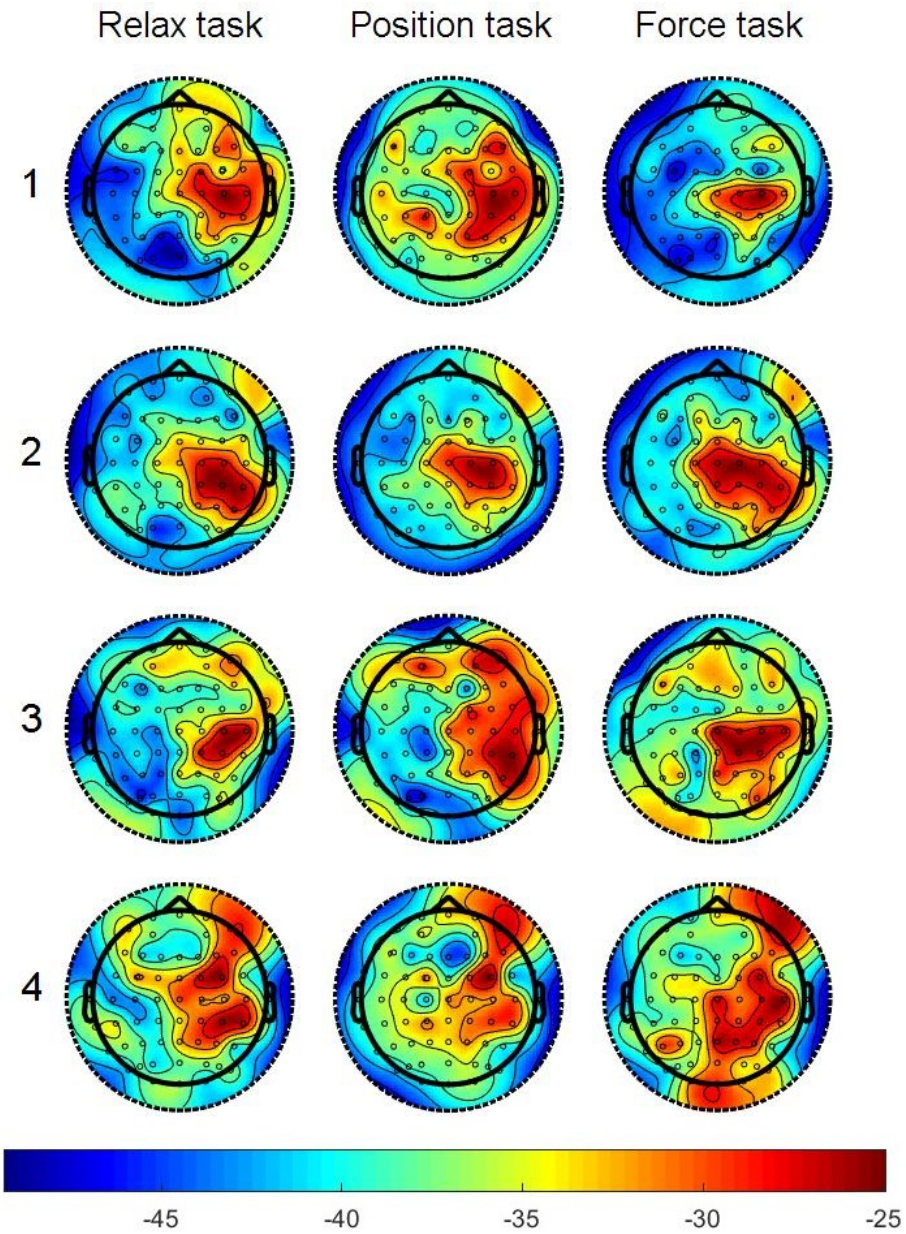
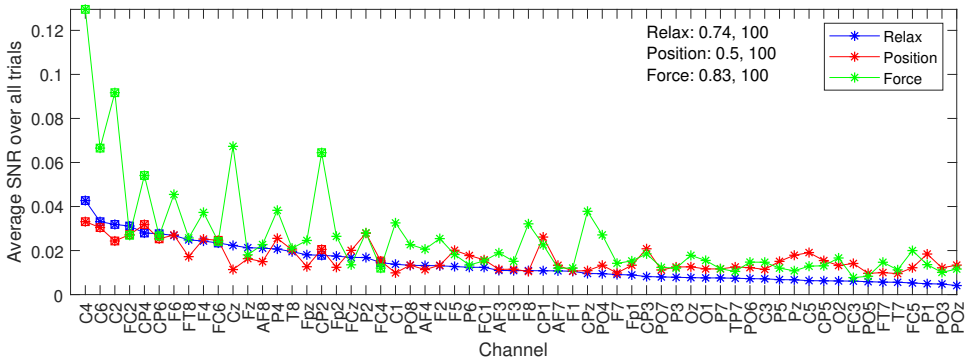
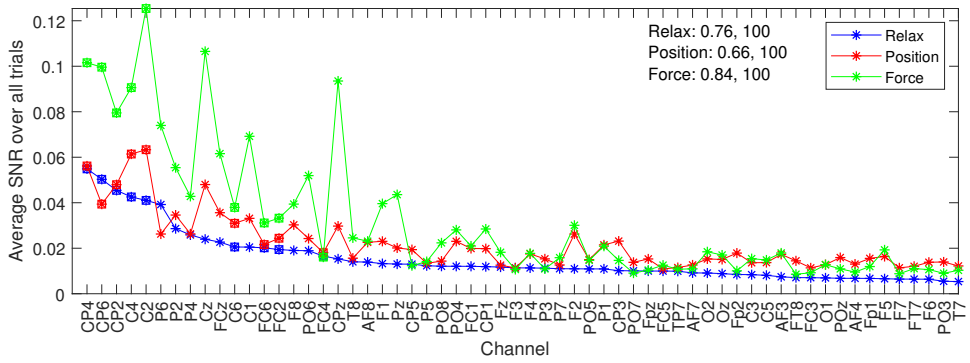


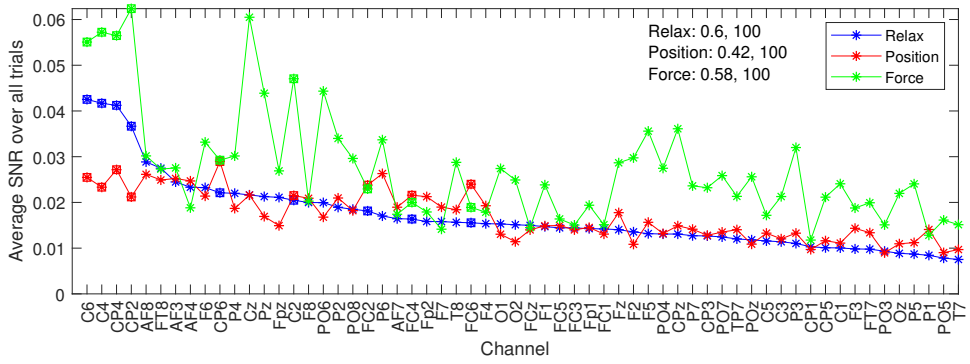
Figure 27: SNR topographical plots of patient 10.



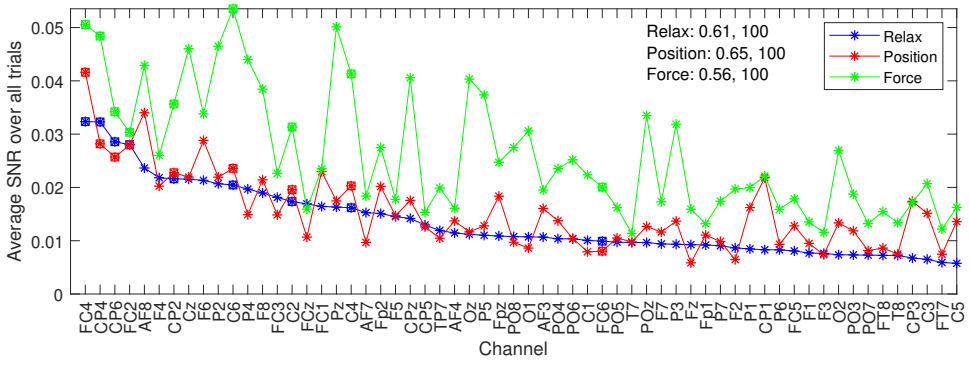
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 28: SNR plotted against channel label for patient 10.

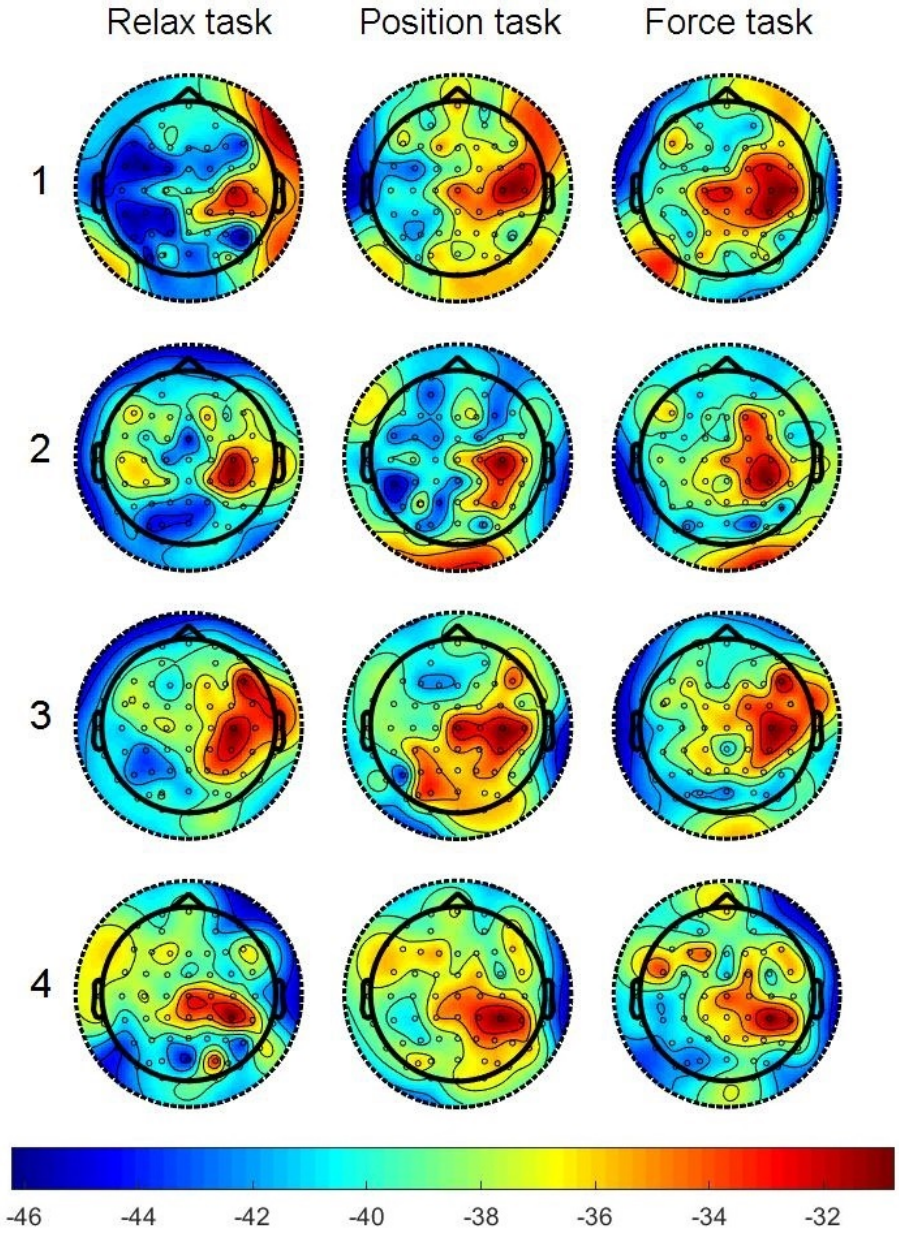
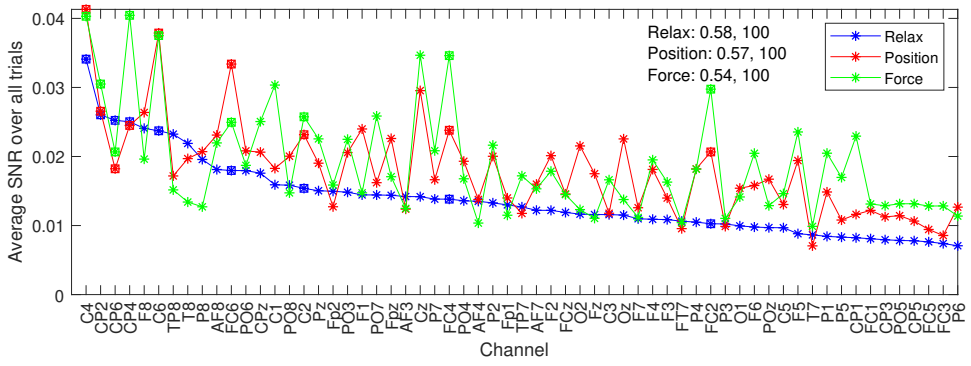
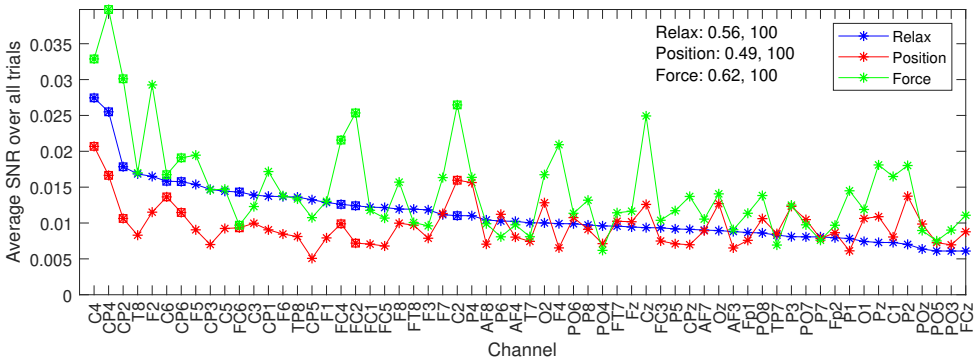


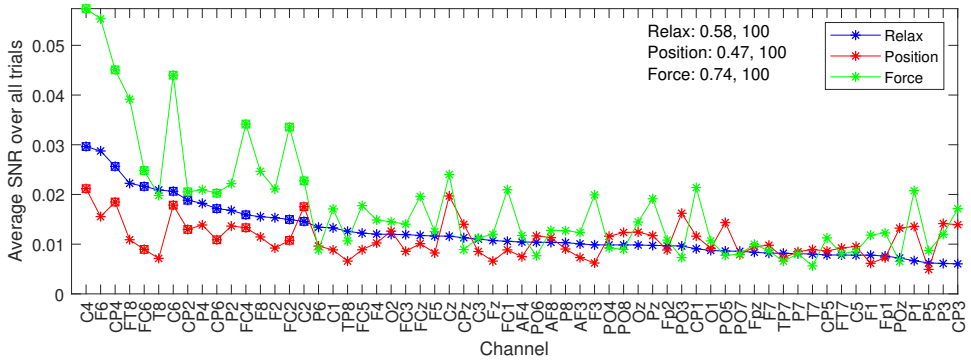
Figure 29: SNR topographical plots of patient 11.



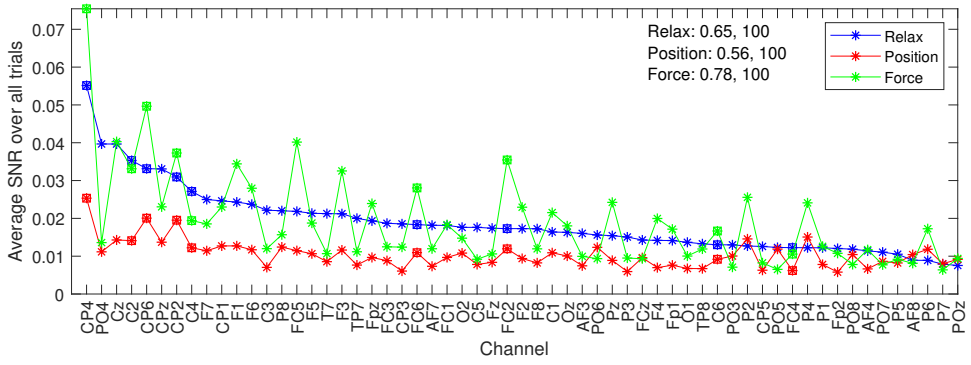
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 30: SNR plotted against channel label for patient 11.

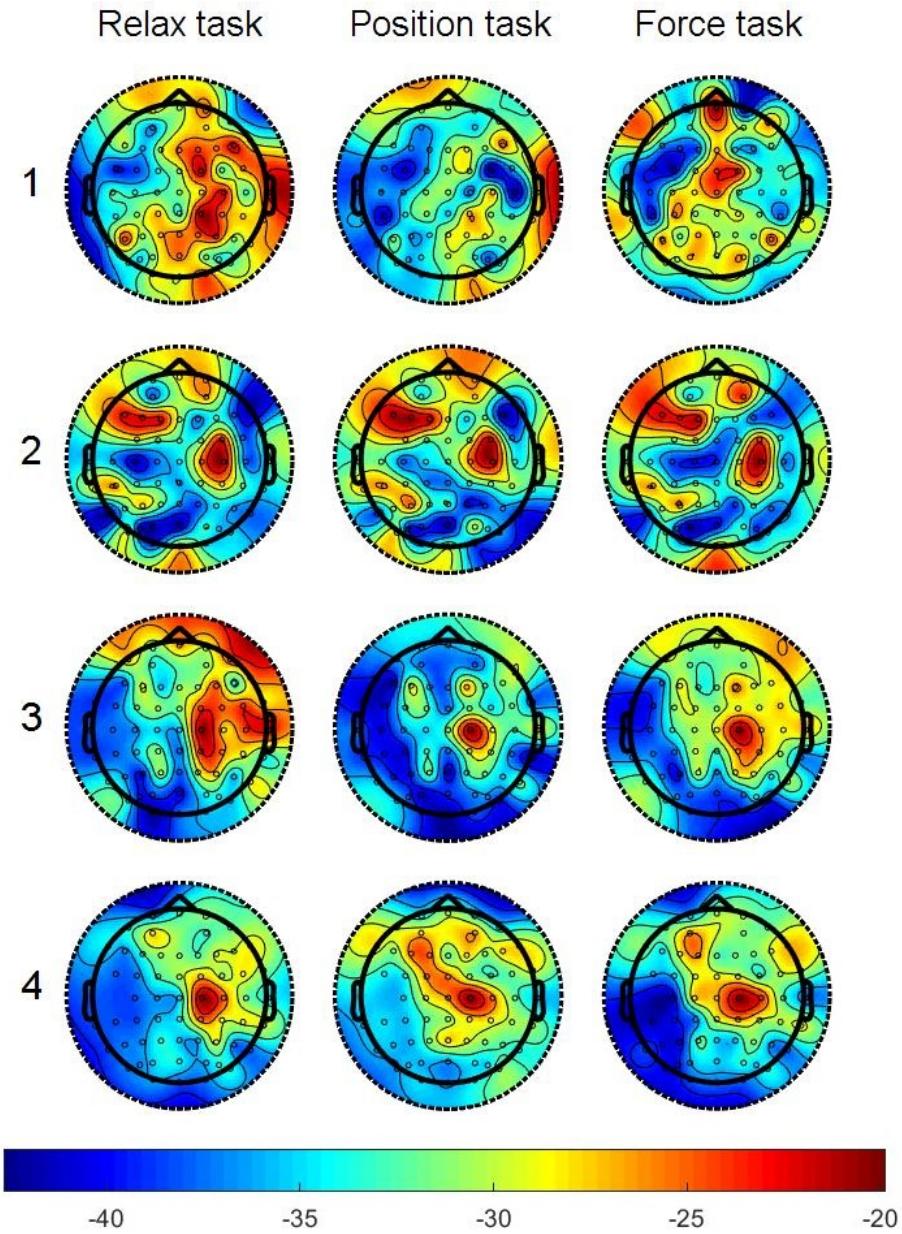
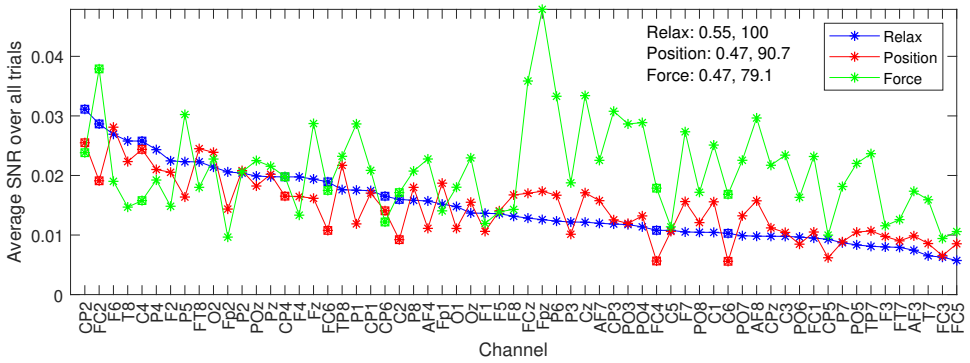
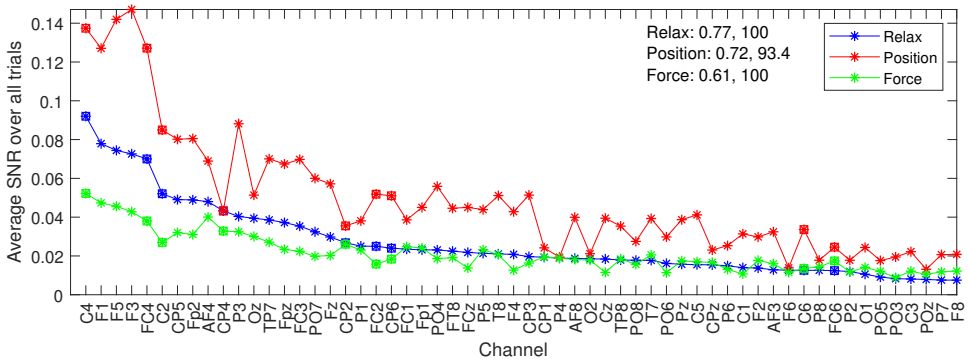


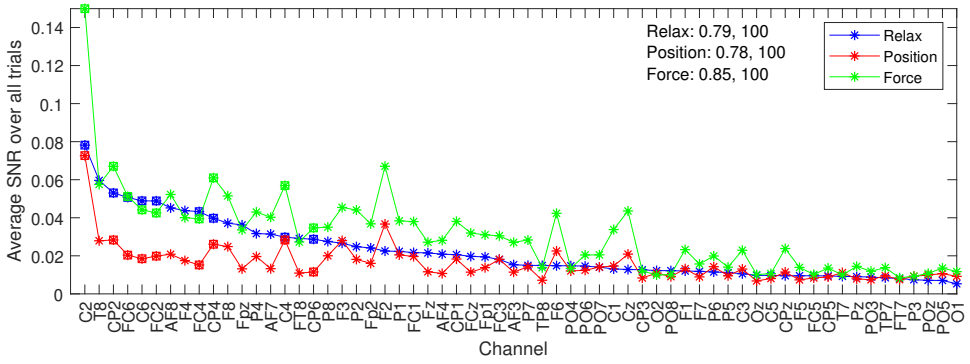
Figure 31: SNR topographical plots of patient 12.



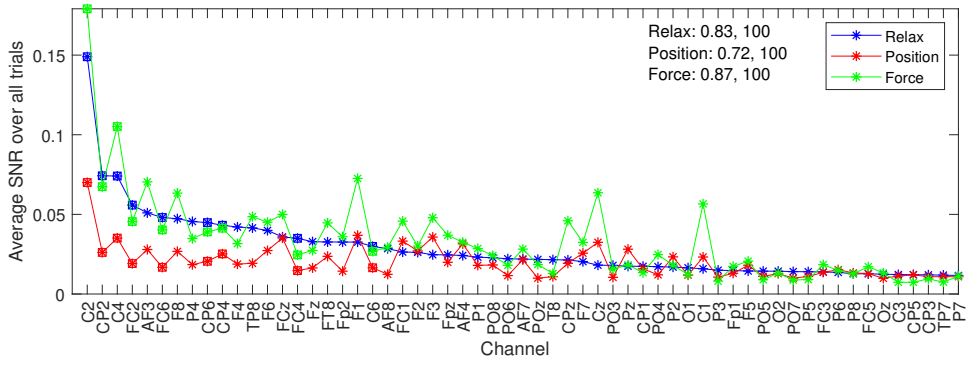
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 32: SNR plotted against channel label for patient 12.

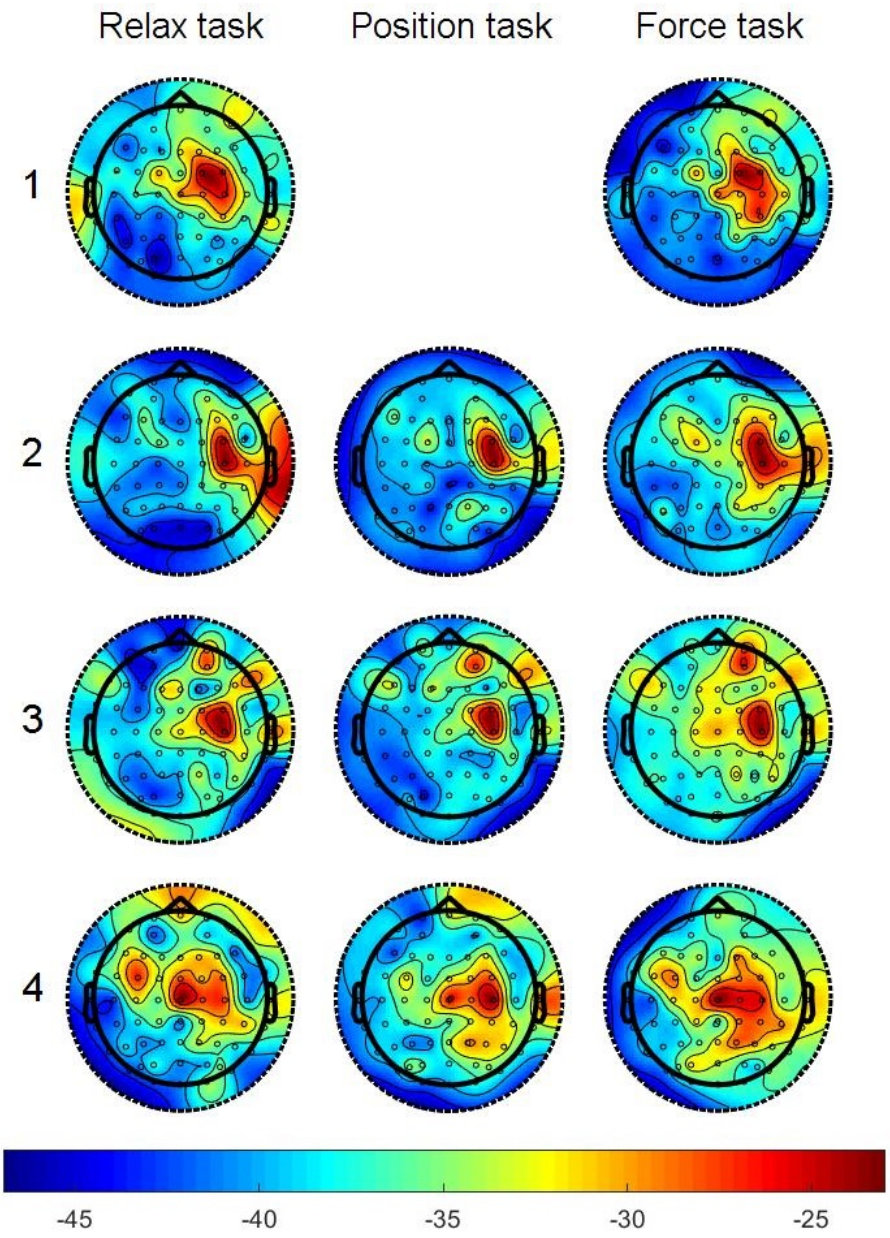
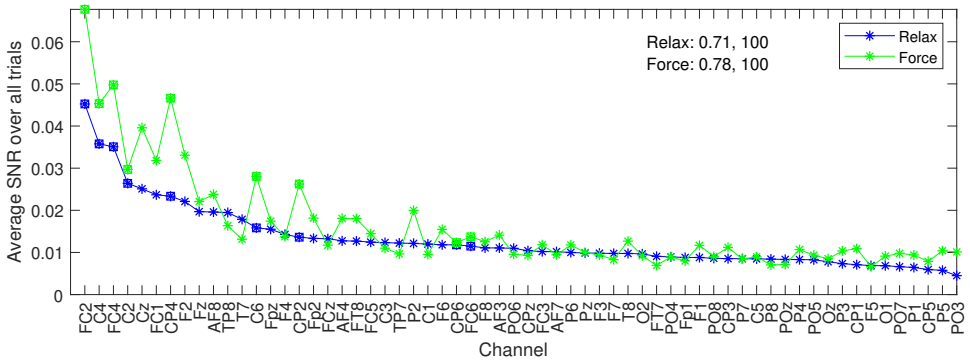
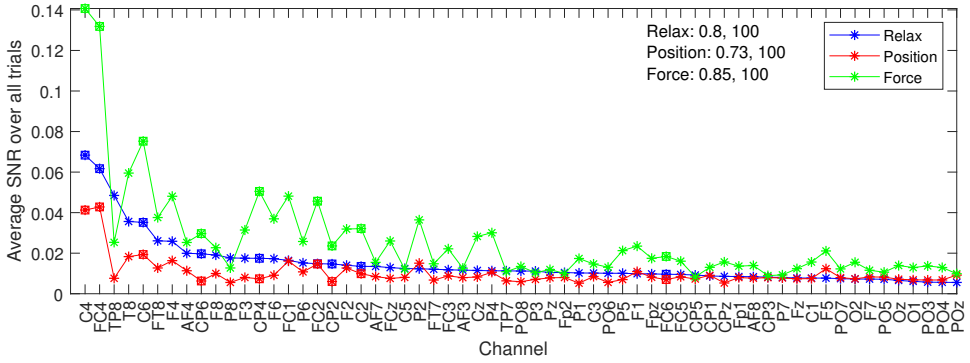


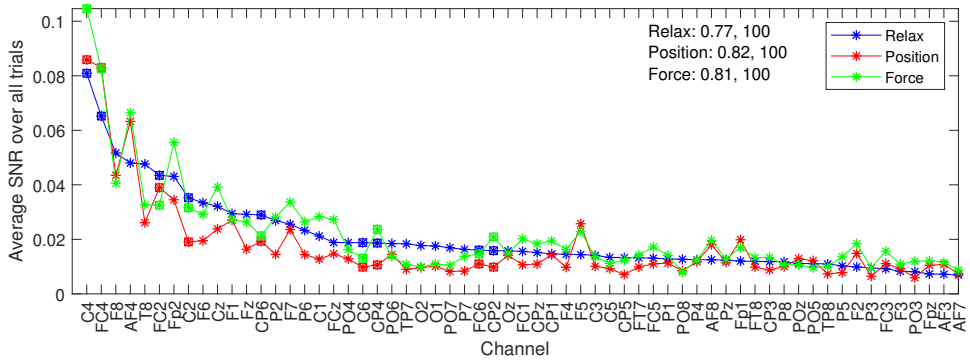
Figure 33: SNR topographical plots of patient 13.



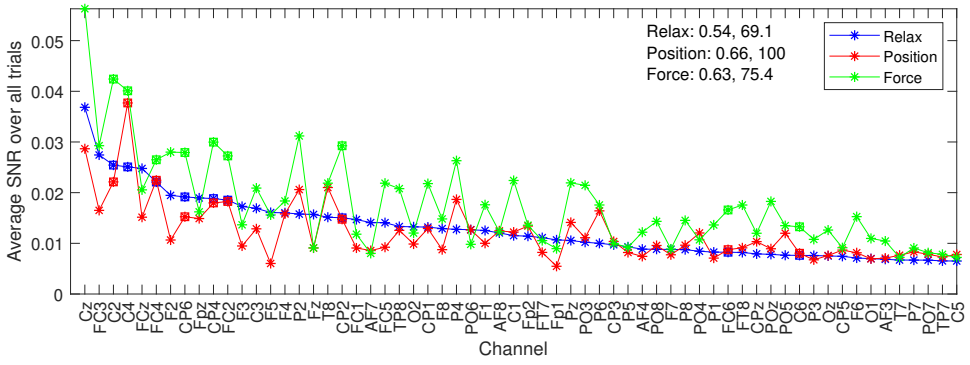
(a) Measurement 1



(b) Measurement 2



(c) Measurement 3



(d) Measurement 4

Figure 34: SNR plotted against channel label for patient 13.