Dynamics of a Stimulation-evoked ECoG Potential During Stroke Rehabilitation
A Case Study

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Abstract: Cortical stimulation is being investigated as a possible tool to support stroke rehabilitation. In particular the analysis of stimulation-evoked neural activity during the rehabilitation process might be helpful to gain a better understanding of the brain reorganization associated with functional recovery after stroke. In this paper, the stimulation-evoked brain activity from a patient with implanted epidural electrodes undergoing an intervention using of brain-computer interfaces combined with cortical stimulation for stroke rehabilitation has been analyzed. We identified a component of the evoked cortical activity that exhibited several characteristics that have not been described before: A significant latency decrease over the course of the rehabilitation training, a significantly smaller latency if the patient attempted to move his paralyzed hand compared to rest and a significant correlation of the latency with the spectral power of the ECoG signal. In addition to the latency, other parameters such as the peak amplitude of the evoked activity were tested as well, but showed a smaller effect size. We hypothesize that such "dynamic" components of the evoked activity that appear to be correlated with the rehabilitation process and the ongoing brain signal could be a target for future closed-loop stimulation systems.

1 INTRODUCTION

Brain stimulation is a powerful tool for clinical practice and research for several reasons: First, stimulation is thought to modulate the activity of the stimulated brain area. This makes it useful for example for the treatment of chronic pain (Tsubokawa et al., 1991) and it is also investigated for stroke rehabilitation (Hummel and Cohen, 2006). Secondly, if one measures the cortical responses (cortico-cortical evoked potentials, CCEPs) to short stimulation pulses, one can derive information about the functional and effective neural connectivity (Matsumoto et al., 2004) within the brain.

It is important to note that these evoked potentials provide a stable measure: At least for transcranial magnetic stimulation (TMS) and EEG, it has been shown that the evoked cortical response is reproducible from session to session (Lioumis et al., 2009; Casarotto et al., 2010). Thus, observed changes in the evoked activity between sessions give an indication that general changes in neural connectivity might have happened over time. However, there is considerable variability in the shape of the response within the same session, even if constant stimulation parameters are used. Some of the variance of the neural responses to a certain set of stimulation parameters can be explained by the concept of cortical excitability: How easily a brain area is activated by stimulation varies for example depending on the task of the stimulated person (Nikulin et al., 2003; Morishima et al., 2009) or the state of consciousness (Massimini et al., 2005). Task-dependent differences in the evoked activity within a session might therefore help to illuminate the role the stimulated brain area and the area where the answer is recorded play in the processing of the task.

These points make the analysis of such

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stimulation-evoked potentials very interesting in the context of motor recovery after stroke: Rehabilitation treatments can induce cortical reorganization (Liepert et al., 2000) which should be accompanied by observable changes in the evoked neural activity, motivating the use of these potentials to monitor the reorganization process. More information about the processes behind such "dynamic" components of the evoked activity can be gained, if the stimulation is then applied while the patient performs different tasks. The task-dependent behavior could then help to identify, which processing steps within the brain have been influenced by the treatment.

Such an improved understanding of the interaction between stimulation and brain reorganization might lead to novel treatment options for the patients. For example, it has been suggested that closed-loop stimulation for stroke rehabilitation might be more effective than the current open-loop paradigms (Plow et al., 2009). One could envision a closed-loop paradigm where stimulation parameters are adapted to the ongoing brain activity in order to closely control evoked potentials connected to the treatment, an approach which has been shown to be feasible in an animal model (Brugger et al., 2011). A necessary prerequisite in order to realize such a system for human patients is that there has to be an influence of the measurable prestimulus neural activity on the stimulation-evoked potential. For motor-evoked potentials (MEPs), conflicting results are reported in the literature, with some studies concluding that the prestimulus spectral power or coherence of the EEG influences the MEP amplitude (e.g. (Schulz et al., 2013)), while other studies fail to find such a relationship (Mitchell et al., 2007; van Elswijk et al., 2010). In the case of evoked cortical activity, a relationship between the amplitude of slow oscillations during sleep and the amplitude of the evoked activity has been described (Bergmann et al., 2012), but during wakefulness, where the cortical responses to stimulation vastly differs from those during sleep (Massimini et al., 2005), no similar influence has been reported.

In our work with hemiparetic stroke patients who underwent implantation of epidural electrodes for the investigation of the combination of brain-computer interfaces and cortical stimulation for stroke rehabilitation (Walter et al., 2009), we analyzed the CCEPs in several experiments over the course of the intervention. In this paper we present results from one patient with a paralyzed hand where we found a component of the evoked cortical activity after epidural electrical stimulation which exhibited an interesting behavior: The latency of this component decreased over the course of the treatment and was significantly depending on whether the patient attempted to move the paralyzed hand or not. We also show that there was a significant correlation between the latency of the component and the spectral power of the ECoG signal before the stimulus. This study provides novel insights into stimulation-evoked potentials, because it is the first time that such an analysis is conducted with (i) a stroke patient who (ii) participated in the same experiment repeatedly over several weeks while (iii) undergoing an intervention attempting to induce neural reorganization using (iv) implanted electrodes for recording and stimulation. Almost all other studies on this topic are conducted with healthy participants and thus restricted to the use of noninvasive methods such as combined EEG and TMS.

2 MATERIALS AND METHODS

2.1 Patient

Patient P1 (male, 56 years old) had suffered a stroke in the right hemisphere 80 months prior to the study, leading to paralysis of the left hand. He was implanted with 16 epidural electrodes (Resume II, Medtronic, Fridley, USA) on 4 strips, arranged in a 4x4 grid covering parts of the primary somatonsensory (S1), primary motor (M1) and premotor cortex (PMC). The grid was centered over the MEP hotspot for the extensor digitorum communis muscle as determined by a TMS mapping (Wassermann et al., 2008) before the surgery. More details on the patient and the electrodes can be found in (Walter et al., 2012). The electrode layout is shown in figure 1 (left).

The external connections to the electrodes were present for four weeks and then internalized in a second surgery. During these 4 weeks, the patient received daily rehabilitation sessions and participated also in the experiment reported in section 2.4.

2.2 Electrophysiological Recording

ECoG was recorded with a monopolar amplifier (BrainAmp DC, BrainProducts, Munich, Germany) with a sampling rate of 1000 Hz and a high-pass filter with a cutoff frequency of 0.16 Hz. ECoG was recorded from all epidural electrodes, with the exception of the stimulation electrode and one electrode over the somatosensory cortex which was used as the reference. In the first session, channel 1 in the setup of figure 1 was used; in all following sessions channel 4. Apart from the ECoG, EMG was recorded as well on

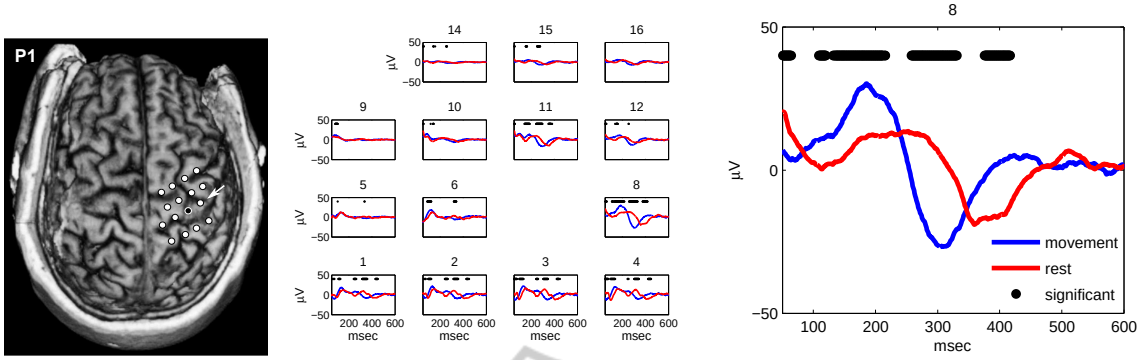

Figure 1: Left: Overlay of the epidural electrode positions with the MRI of P1. White circles: recording electrodes, black circle: stimulation electrode. Channel 1 is in the lower left corner, channel 4 in the lower right corner, channel 16 in the upper right corner and so on. White arrow: Position of channel 8. Center: Average CCEP for stimuli in the movement (blue) and rest (red) phase for all channels, 50 - 600 msec after the pulse. Black dots mark samples with a significant difference in the amplitude between conditions. Channel 13 on the upper left corner was the reference, therefore it is missing. Data stems for the third session with P1. Right: Zoom on the averaged CCEPs per condition for channel 8.

the left hand and arm, but it did not play a role for this analysis. A 50x90 mm adhesive electrode placed under the left clavicle of the patient served as the ground electrode for the recording. Prior to further analysis, the ECoG data was re-referenced to channel 13 on the frontomedial corner of the electrode grid.

2.3 Cortical Stimulation

For epidural electrical stimulation we used an STG 4008 stimulus generator (MultiChannel Systems, Reutlingen, Germany), capable of a maximum output current of 16 mA. Stimulation was applied with single anodal biphasic rectangular symmetric pulses with a length of 500 μsec and an intensity of 7 mA. The adhesive electrode on the left clavicle of the patient also served as the cathode for stimulation. The intensity of 7 mA was selected because a single pulse with this intensity consistently evoked small MEPs on the left extensor digitorum communis (EDC) muscle of the patient. The stimulation pulses were given continuously throughout the experiment with a fixed inter-stimulus interval of 2 seconds and a small jitter of $\pm$ 40 msec.

2.4 Experiment

The data analyzed here stems from the open-loop stimulation experiment described in (Walter et al., 2012). In short, the patient was sitting in a chair with his left arm and hand fixed to a commercially available rehabilitation device (Tyromotion Amadeo HTS, Graz, Austria). This orthosis was capable of opening and closing the paralyzed hand of the patient.

The task of the patient was to attempt to open his paralyzed hand on cue. Each trial consisted of three phases: preparation (2 sec), movement (6 sec) and rest (8 sec). During *preparation*, the participant received an auditory cue but was instructed to wait with the execution until the "Go!" command was given at the start of the *movement* phase. During the *movement* phase, starting with a closed position of the left hand, the participant had to try to open the left hand until the end of the movement phase. At that point, another auditory cue ("Relax!") was given. During the *rest* period, the hand of the participant was returned to its original closed position which took about 2-3 seconds and the participant was instructed to relax. This task design was adapted from (Ramos-Murguialday et al., 2013) who used it in a noninvasive BCI-guided rehabilitation study with stroke patients, but without stimulation.

During the movement phase, the spectral power of the ECoG recorded on channels over S1 and M1 between 16 and 22 Hz was extracted and used as input for an adaptive linear classifier to detect online when the patient is trying to move the paralyzed hand. This makes use of the well-known event-related desynchronization (Pfurtscheller and Lopes da Silva, 1999) of sensorimotor and β rhythms during movements. If such an intention was found, the orthosis continued to open the hand, otherwise it was stopped. For the computation of the spectral power in the presence of stimulation artifacts, the methods from Walter et al. (2012) were used.

Over the course of 4 weeks, the experiment was repeated with the patient weekly, 4 times in total. Per session, between 42 and 48 trials were conducted. Regarding stimulation, between 130 and 143 stimuli were applied during the movement phases and between 174 and 200 stimuli within the rest phases. There are more stimuli in the rest phase due to the greater length of this phase compared to the move-

Table 1: CCEP parameter for measured signal $s(t)$.

Parameter	Computation
Latency τ	Woody's method
Positive peak	$\max\{s(\tau+t), -200 \leq t \leq 200\}$
Negative peak	$\min\{s(\tau+t), -200 \leq t \leq 200\}$
Area	$\sum_{t=\tau-200}^{\tau+200} s(t)$
Absolute area	$\sum_{t=\tau-200}^{\tau+200} \lvert s(t)\rvert$

Table 2: Number of stimuli in the analysis.

Session	Movement	Rest
1	141	166
2	133	159
3	128	169
4	140	196

ment (8 sec vs. 6 sec).

For each of these stimuli, the spectral power of the prestimulus data and several parameters for the CCEP were extracted.

2.5 Parametrization of CCEPs

After visual inspection, the late CCEP was most pronounced on channel 8, thus this channel was used for further analysis (see figure 1). The latency of the CCEP component was estimated with Woody's method (Woody, 1967): A template was constructed by averaging the evoked potentials from stimuli in the movement phase for the time window between 100 and 600 msec after the stimulation pulse. The cross-correlation of this template with the evoked waveforms then yields the latency of the component for each individual stimulus.

Other extracted parameters are the amplitude of the strongest positive and strongest negative peak, the sum of all amplitudes and the sum of the absolute amplitudes (table 1). Visual inspection revealed that the CCEP was contained within an area of $\pm$ 200 msec around the strongest negative peak. Thus, the peak and area parameters were computed in this range. 11 stimuli of the rest phase of session 1 and 13 of the rest phase of session 2 were removed from further analysis, because no proper fit of the template could be obtained for them, leading to non-meaningful lag estimations. Furthermore, if no positive or negative peak could be found, the stimulus was removed as well from further analysis. Due to this condition, 23 more stimuli were removed. The number of stimuli per condition and session that entered the analysis are given in table 2.

2.6 Spectral Analysis

We used autoregressive (AR) models to estimate the spectral power before each stimulus. To this end, one second of the signal directly before the stimulus was extracted and an AR model of order 50 was fitted to the data and evaluated at frequencies between 5 and 100 Hz in steps of 1 Hz.

2.7 Statistical Analysis

The dependency of the CCEP parameters on the factors *session* and *movement condition* was assessed with a two-way ANOVA because we found no strong deviations from normality in the residuals. *Post hoc* tests were conducted with unpaired t tests.

We performed permutation tests to investigate whether there is a significant correlation between the prestimulus spectral power and parameters of the evoked component and which time points of the poststimulus signal have significantly differing amplitudes for movement and rest.

The Spearman correlation coefficient ρ was used as a nonparametric measure of a monotonous relationship between the spectral power and the CCEP parameters. The significance of the correlation was assessed with a permutation test, repeated 3000 times. In each repetition k, $\rho_{f_i,k}$ between the spectral power values at each frequency $f_i \in 5,\ldots,100$ Hz and a random permutation of the CCEP parameter values was computed and $m_k = \max(|\rho_{f_i,k}|)$ was extracted and aggregated in the set $M = \{m_k\}_{k=1,\ldots,3000}$. The significance threshold for $|\rho|$ at the $\alpha = 0.05$ level was set as the value of M corresponding to the one-tailed (1-α)100^{th} percentile of M.

Significant differences in the evoked activity between the movement and the rest phase of the trial (shown for an example in figure 1) were assessed in a similar way: For each time point, Cohen's d for unequal sample sizes was used as a measure for the difference between the stimuli in each condition. The condition labels were permuted 3000 times and $d_{t_i,k}$ was computed for each repetition k and poststimulus time point t_i. The maximum $m'_k = \max(d_{t_i,k})$ of each repetition was stored in a set $M' = \{m'_k\}_{k=1,\ldots,3000}$, yielding the significance threshold for d. However, in contrast to above, because this procedure was performed for all recording channels, the threshold was taken at the $\alpha = \frac{0.05}{C}$ level, where C is the number of recording channels. In the case displayed in figure 1: C=14.

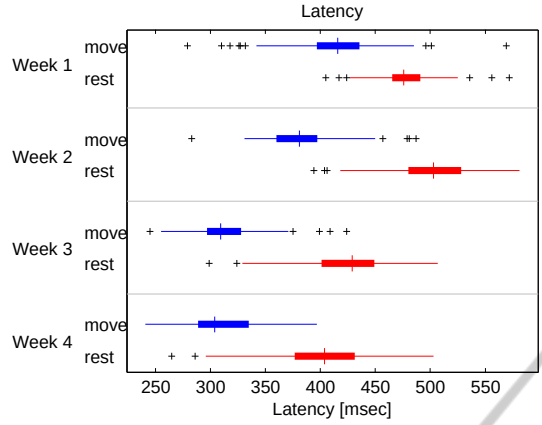

Figure 2: Single-trial latency of the evoked component, grouped by condition and session.

3 RESULTS

3.1 Influence of Time and Movement Condition

The patient participated in the experiment 4 times with a time difference of 1 week between sessions. We found a significant, consistent reduction in the latency over time and a strong difference between conditions (figure 2). This was confirmed by a two-way ANOVA with factors *condition* and *session*, where a significant effect was found for the *condition* ($F(1,1218) = 2244.6$, $p < 0.001$), the *session* ($F(3,1218) = 518.5$, $p < 0.001$) and the interaction between the two ($F(3,1218) = 41.5$, $p < 0.001$). Within each session, the latency during movements was consistently smaller than during rest (one-sided t tests, all $p < 0.001$). For the other parameters, the factor *session* was always significant and the *condition* for the area and the negative peak amplitude. The interaction between both factors was significant for the area and the absolute area, but not the peak measures. The detailed ANOVA tables and graphs for these parameters are found in appendix 4. The comparison of the graphs in figure 4 with figure 2 make it clear that the effect size for the latency is much greater than for the other parameters.

3.2 Influence of Prestimulus Spectral Power

The left part of figure 3 shows that there is a significant correlation between the spectral power before the stimulus and the extracted CCEP parameters, especially in the range of 10-40 Hz, roughly encompassing parts of the α band and the β band. Across sessions, this correlation is best preserved for the latency and to alesser extent for the area. However, one might argue that this correlation is simply an effect of a switch in the ”brain state” between the *movement* and the *rest* phase. It is well known that the spectral power of the brain rhythms differs between these tasks (Pfurtscheller and Lopes da Silva, 1999) and also that the excitability of the motor cortex is higher during movements than during rest (Fadiga et al., 1999). Thus, when taking all stimuli into account, this correlation might simply be an epiphenomenon of the changing brain state.

For this reason, we also looked at the CCEPs when only stimuli within the movement phase are taken into account (figure 3, right). We found that in this case, there is still a significant reproducible correlation present for the latency, again most pronounced for the β band, but that it vanishes for the other parameters. Because no direct change of the brain state is expected here, the correlation could indicate a direct influence of the spectral power of the ongoing brain activity on the component latency.

4 DISCUSSION

In patient P1, we identified a component of the stimulation-evoked cortical activity which exhibited an interesting behavior. First of all, in the first experimental session, the peak of this component occurred with a latency of 447.84 ± 43.66 msec (mean $\pm$ std). Although the literature characterizing CCEPs from epidural stimulation is scarce, TMS-evoked EEG responses in healthy persons last only for up to 300 msec after the pulse (Ferreri et al., 2011). If we expect a more or less similar behavior for epidural stimulation, such a late component is certainly an oddity. Secondly, we found that there was a clear difference in the shape and latency of this component depending on whether the patient was attempting to move the paralyzed hand (*movement* phase) or resting (*rest* phase). Thirdly, because the experiment was repeated weekly over the course of 4 weeks, we were able to observe the evolution of this potential while the patient performed the rehabilitation training. We found a coherent reduction of the latency across sessions. Taken together, this means we have found an evoked potential which had a possible relationship to the motor system of the paralyzed limb (difference between movement and rest), had very atypical characteristics at first (high latency) which became less atypical over the course of the rehabilitation training (reduction in latency across time). Thus, this po-

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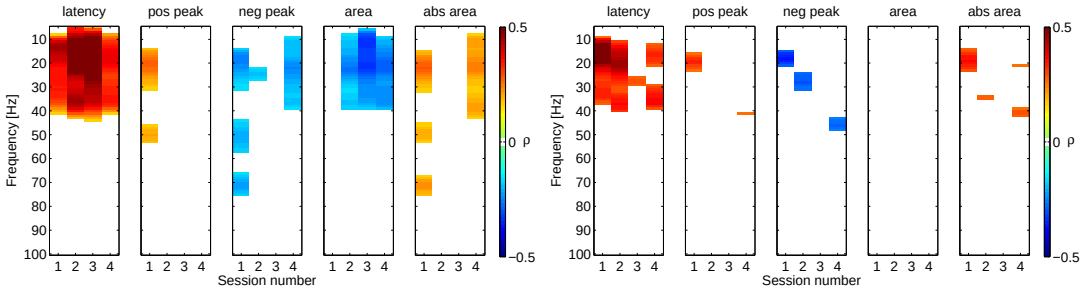

Figure 3: Significant correlations between parameters of the CCEP and the prestimulus spectral power. Left: all stimuli. Right: Only stimuli during the movement phase.

tential might serve as a correlate for rehabilitation. Furthermore, the analysis showed a significant relationship between the prestimulus spectral power and the latency of the component. The positive correlation between the latency and the spectral power was most prominent in the β-band, meaning that higher β-power is associated with a longer latency. This is consistent with studies on the relationship between EEG and TMS-evoked MEPs that implicated β-band power as an inhibitory mechanism in the motor system (Schulz et al., 2013) and also with the event-related desynchronization of β oscillations during attempted movements. On the level of CCEPs, however, such a relationship has not been reported, yet. An earlier study with combined EEG and TMS had identified movement-related changes in the evoked brain activity for an N100 component (Nikulin et al., 2003). They demonstrated a decrease in the amplitude and an increase in latency for the N100 during movement compared with rest and hypothesized that the N100 is an inhibitory response that is suppressed during movements. The evoked potential described here exhibits the opposite behavior at least for the latency, thus we can speculate that it might represent an excitatory response.

From this, a closed-loop system could be feasible which uses online spectral analysis to predict the latency of the evoked activity, stimulating only if this prediction is within a predefined range in order to reduce the variance of the stimulation effect. It would be very interesting to see whether such an optimized closed-loop stimulation protocol had an impact on the recovery of motor function.

Unfortunately, the external connection with the implanted electrodes of the patient had been removed in a second surgery before further experiments on this issue with the patient could take place. Although the experiment was repeated in two more chronic stroke patients, no comparable CCEP component could be identified. It is unclear whether the occurrence of the component analyzed here was just due to the specific pathophysiology of patient P1 or if it might be reproducible in more patients. For this reason, it would be very interesting to perform this or a similar experiment with other stroke patients undergoing rehabilitative training. It might not be necessary to use implanted electrodes for these experiments as combined EEG and TMS might suffice. One great advantage of the implanted electrdoes is, however, that these are fixed in place, eliminating the possibility that the sensitivity of evoked potentials to the stimulation position (Casarotto et al., 2010) influences the analysis. Similarly, instead of an online analysis of the brain activity, it might be enough to have the patient perform cued attempts to move the paralyzed limb, as long as one retains the concept of applying single suprathreshold stimulation pulses over the hotspot of MEP generation on the paralyzed limb in the lesioned hemisphere. If the hypothesis is correct that such a late potential is a correlate of the pathological changes after stroke, one should be able to observe a potential with the following characteristics at least for some patients:

- Location over sensorimotor cortex on the stimulated hemisphere
- High latency at the start of the rehabilitation training
- Latency reduces over the course of the training
- Latency and other parameters differ between stimuli during the movement and stimuli during the rest phase.
- Correlation between the prestimulus spectral power and some parameters of the CCEP

If this is confirmed, it might be worthwhile to attempt a closed-loop stimulation experiment as proposed above to control the evoked component.

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APPENDIX

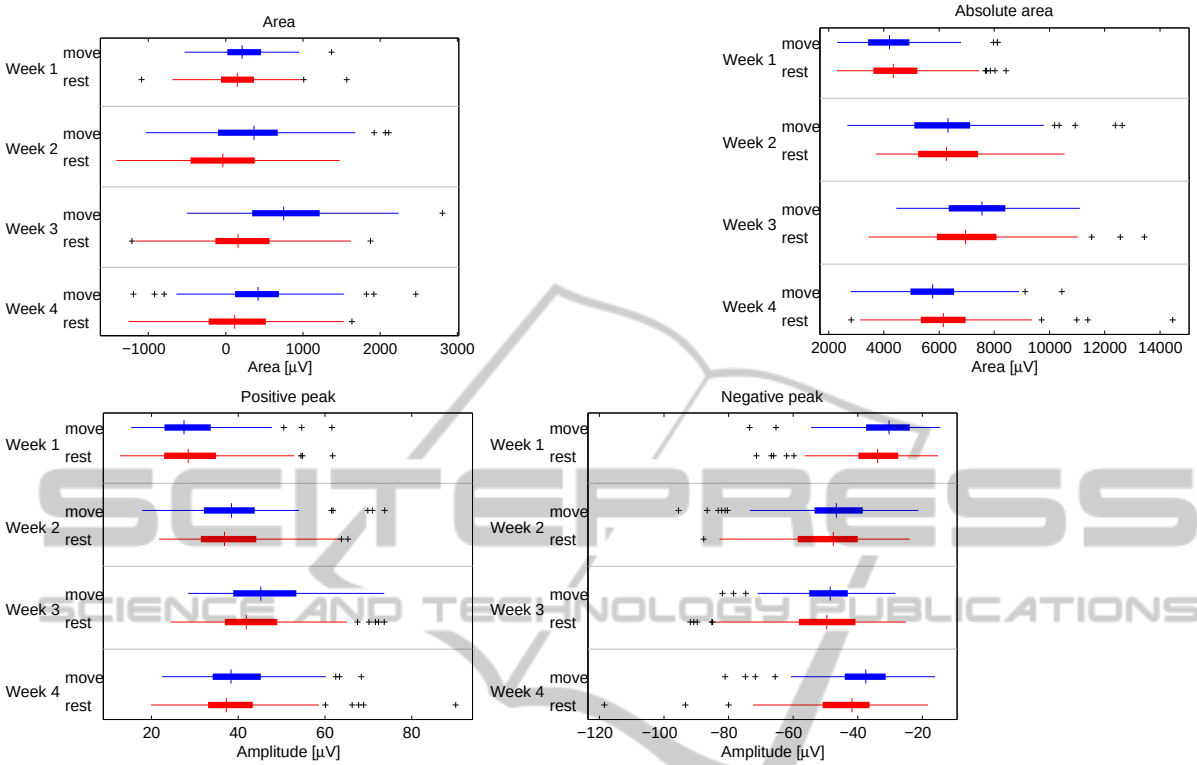

Figure 4: Single-trial parameters of the evoked component, grouped by condition and session.

Table 3: Results of two-way ANOVAs for the CCEP parameters for factors *session* (S), *condition* (C) and the interaction between these (S*C).

Parameter	Factor	df	F(df,1218)	p
Latency	S	3	518.5	< 0.001
	C	1	2244.6	< 0.001
	S*C	3	41.5	< 0.001
Positive peak	S	3	150.93	< 0.001
	C	1	2.16	0.14
	S*C	3	2.18	0.09
Negative peak	S	3	127.64	< 0.001
	C	1	21.26	< 0.001
	S*C	3	1.93	0.12
Area	S	3	21.7	< 0.001
	C	1	119.7	< 0.001
	S*C	3	11.38	< 0.001
Absolute area	S	3	210.29	< 0.001
	C	1	1.40	0.24
	S*C	3	3.15	0.024

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