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High Frequency Oscillations Evoked by Peripheral Magnetic Stimulation

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Abstract— **The analysis of somatosensory evoked potentials (SEP) and / or fields (SEF) is a well-established and important tool for investigating the functioning of the peripheral and central human nervous system. A standard technique to evoke SEPs / SEFs is the stimulation of the median nerve by using a bipolar electrical stimulus. We aim at an alternative stimulation technique enabling stimulation of deep nerve structures while reducing patient stress and error susceptibility. In the current study, we apply a commercial transcranial magnetic stimulation system for peripheral magnetic stimulation of the median nerve. We compare the results of simultaneously recorded EEG signals to prove applicability of our technique to evoke SEPs including low frequency components (LFC) as well as high frequency oscillations (HFO). Therefore, we compare amplitude, latency and time-frequency characteristics of the SEP of 14 healthy volunteers after electric and magnetic stimulation. Both low frequency components and high frequency oscillations were detected. The HFOs were superimposed onto the primary cortical response N20. Statistical analysis revealed significantly lower amplitudes and increased latencies for LFC and HFO components after magnetic stimulation. The differences indicate the inability of magnetic stimulation to elicit supramaximal responses. A psycho-perceptual evaluation showed that magnetic stimulation was less unpleasant for 12 out of the 14 volunteers. In conclusion, we showed that LFC and HFO components related to median nerve stimulation can be evoked by peripheral magnetic stimulation.**

I. Introduction

THE examination of the peripheral and central nervous system by the analysis of somatosensory evoked potentials (SEP) and/or fields (SEF) is an important tool for neuroscientific research and clinical routine [1]. A standard procedure is to noninvasively apply bipolar electric stimuli to the median nerve while simultaneously recording the electroencephalographic (EEG) signals.

The characteristic brain potentials evoked by this stimulation consist of low frequency components (LFC) and high frequency oscillations (HFO) [2], [3], which are generated by different neuronal structures [3], [4], [5].

Although electric stimulation is the most common stimulation technique, it is often reported unpleasant and even painful for the subjects [6]. Furthermore, insufficient and inconsistent moisturization of the electrode pads can influence the electric current density and thus the quality of the stimulation. A disadvantage using bipolar electrodes is the strong limitation that deep or inaccessible nerves cannot be stimulated. Thus, more adequate stimulation techniques for comfortable investigations concerning these nerve structures are necessary.

A possible concept is the use of magnetic stimulation. While transcranial magnetic stimulation (TMS) is already established in medical research and clinical routine for diagnostics as well as therapy, peripheral magnetic stimulation has rarely been employed [7].

In this contribution, we present the results of a study to prove that both LFC and HFO components of the SEP can adequately be evoked by peripheral magnetic stimulation. The study involves 14 volunteers and compares the SEPs after electric and magnetic stimulation using latency and amplitude analysis for the LFCs as well as the HFOs. In addition, the sensation of the stimuli is investigated using psycho-perceptual evaluation.

II. Materials and Methods

A. Test participants

Fourteen healthy volunteers (12 males, 2 females) of ages between 19 and 25 (mean 22.5 years) participated in this study. An introductory conversation assured that volunteers with metal implants, pacemakers, known neurological disorders, pregnancy or long-term medication were excluded. All volunteers gave their written informed consent and the study was proven by the ethic committee of the Friedrich-Schiller-University Jena.

B. Study Design

After a short briefing, the participants were seated on a medical chair with their right arm fixed to a non-conductive mounting, preventing relative movements between stimulation target and stimulator (cp. Fig. 1).

For the bipolar electric stimulation, we used a constant

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Fig. 1. Measurement setup for the peripheral magnetic stimulation using the TMS system. A - non-conductive fixation, B - arm cover, C - figure-8 stimulation coil, D – 128 channel EEG cap, E - ear protection

current high voltage stimulator (DS7A, Digitimer Ltd, Hertfordshire, United Kingdom), which was externally triggered by a function generator (33250A, Agilent Technologies Inc., Santa Clara USA). The stimulation electrodes were initially placed 2 cm proximal to the wrist with the cathode 2 cm proximal to the anode. The point of stimulation was then optimized in terms of increased contraction of the thenar eminence. According to Lesser et al. [6], the stimulation intensity was set to the sum of the motor and sensor thresholds, which were determined individually for each participant at the beginning of the measurement.

For the magnetic stimulation, we used a commercial TMS system (Rapid^2, Magstim Company Ltd, Whitland, United Kingdom) with a figure-8 air-cooled coil (Air Film Coil, Magstim Company Ltd, Whitland, United Kingdom) placed perpendicularly to the median nerve (cp. Fig. 1). The point of stimulation as well as the stimulation intensity were determined in an analogous manner as for the electric stimulation.

The EEG was recorded using a 32-channel commercial EEG amplifier with a sampling frequency of 10 kHz (RefaHS-32, Advanced Neuro Technology B.V., Enschede, The Netherlands). We used a 128-channel EEG cap with an equidistant electrode layout (WaveGuard 128-channel Duke, Advanced Neuro Technology B.V., Enschede, The Netherlands) and shielded signal wires. For signal acquisition, we selected a subset of 32 channels.

In both stimulations, 5550 stimuli were applied with a stimulation rate of 3.7 Hz. The stimulation sequence, which was predetermined by the heating of the TMS coil, was divided into three blocks containing 50 trains with 37 stimuli. The inter-train time was 11.2 s, the inter-block time approximately 5 min. The order of electric and magnetic stimulation was randomly selected separating the volunteers into two groups of equal size.

To evaluate the sensation, we employed psycho-perceptual evaluation based on a labeled nominal five-point scale from +2 (very good) to -2 (very bad). In the test, the volunteers were asked to rate the sensation of both kinds of stimuli on the skin and in the tissue.

To avoid acoustic evoked potentials resulting from the trigger-synchronous mechanic sounds of the TMS-system, white noise sound masking with in ear-phones was applied. Additionally, the acoustic perception of the click sound was damped with a standard ear protector (cp. Fig. 1).

Since the nerve conduction velocity strongly depends on the temperature, the arm was covered to avoid cooling and the skin temperature was controlled periodically.

C. Data Analysis

The recorded EEG data were visually checked and artifacts were manually marked and eliminated using ASA-Lab software (Advanced Neuro Technology B.V., Enschede, The Netherlands). Subsequently, the single trials were averaged using the interval from -80 ms (prestimulus) to +100 ms (poststimulus). The averaged datasets were exported and further analysis was performed in Matlab (The MathWorks Inc., Natick, Massachusetts, USA). At first, the stimulus artifact resulting from the TMS system was removed by linear interpolation between -1 ms and +5 ms. Baseline correction was performed based on the interval from -80 ms to -10 ms. Subsequently, three datasets (LFC only, HFO only, LFC+HFO) were extracted using zero phase bandpass filters according to Table I. The filter parameters were selected according to the literature [4], [5].

TABLE I
DATASET FILTER PARAMETERS

Dataset	Filter type	Order	Frequency range
LFC	IIR Butterworth	94	10-300 Hz
HFO	IIR Butterworth	66	450-750 Hz
LFC+HFO	IIR Butterworth	222	10-750 Hz

In order to determine the amplitude and latency of the low and high frequency components, we used the peak of the N20 component and the Hilbert-transformed HFOs, respectively.

III. Results

The SEPs for both stimulations are displayed in Fig 2a and 2b. The N20 component of the LFC is visible after electric as well as magnetic stimulation in recordings of all 14 volunteers (cp. Fig. 2c and 2d). The N20 component was identified with maximum amplitude for 13 out of the 14 volunteers in channels LB4, LA5, and LL10. Hence, detailed amplitude and latency analysis for the N20 component was performed with focus on these channels. The determined amplitudes and latencies were averaged over all volunteers. The results are summarized in Table II. It is obvious that the applied magnetic stimulation leads to decreased amplitude and increased latency.

A Kolmogorov-Smirnov test confirmed the amplitudes and latencies to be normally distributed. Thus, a dependent t-test for paired samples was applicable to proof the significance of the differences between the values obtained after electric and magnetic stimulation.

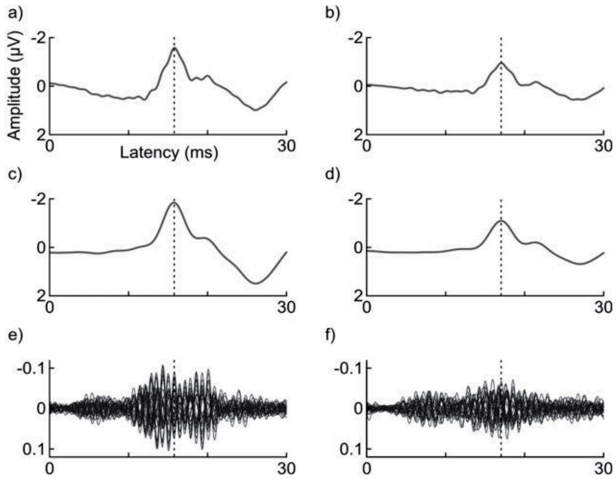

Fig. 2. Averaged and filtered EEG of a single volunteer: a), c), and e): after electric stimulation; b), d), and f): after magnetic stimulation; a) and b) LFC+HFO in channel LL10; c) and d) LFC in channel LL10; e) and f) Butterfly plot of HFO after artifact correction. The position of the peak of the N20 component is marked by a vertical, dotted line.

The p-values for the amplitudes were in the range of 2.53×10^{-5} to 5.78×10^{-5}, thus indicating a highly significant difference. For the latencies p-values between 1.42×10^{-5} and 3.41×10^{-5} were obtained showing that the latencies after magnetic stimulation were significantly larger than these after electric stimulation.

TABLE II
AMPLITUDE AND LATENCY OF THE N20 COMPONENT

		Amplitude in µV		Latency in ms	
Stimulation	Channel	Mean	SD	Mean	SD
electric	LB4	-1.03	0.53	17.66	1.03
electric	LA5	-1.32	0.71	17.84	1.01
electric	LL10	-1.17	0.59	17.94	0.96
magnetic	LB4	-0.56	0.34	18.42	1.11
magnetic	LA5	-0.75	0.44	18.56	0.98
magnetic	LL10	-0.68	0.39	18.62	0.95

HFOs were visible after the electric as well as the magnetic stimulation for all volunteers. In Fig. 2e and 2f, the EEG of a single volunteer is plotted for a frequency range of 450 to 750 Hz. The amplitudes of the HFOs increase close to the N20 component (cp. Fig. 2e and 2f). In Fig. 2a and 2b, the superposition of the HFOs on the increasing and decreasing flanks of the N20 is visible as small variations. For five volunteers, it was possible to distinguish the HFOs on these flanks after electric stimulation (cp. Fig. 2e). This was not possible for the magnetic stimulation (cp. Fig. 2f).

A time-frequency analysis on the LFC+HFO datasets was performed using a Multichannel Matching Pursuit (MMP) approach [8]. The first 30 atoms were used for representing the signal in the range between 0 ms and +30 ms. Afterwards, the two atoms corresponding to the N20 component and the high frequency oscillations were separated. The results confirm the superposition of the HFO and the increasing flank of the N20 component (cp. Fig. 3). By comparing the N20 component of Fig. 3a and 3b again a delay is visible after the magnetic stimulation. The HFO has a more limited frequency range (approx. 500-650 Hz) but a wider extension in time (approx. 12-21 ms) during magnetic stimulation (Fig. 3b) compared to the atom for the electric stimulation (approx. 300-650 Hz and 11-14 ms) (Fig. 3a).

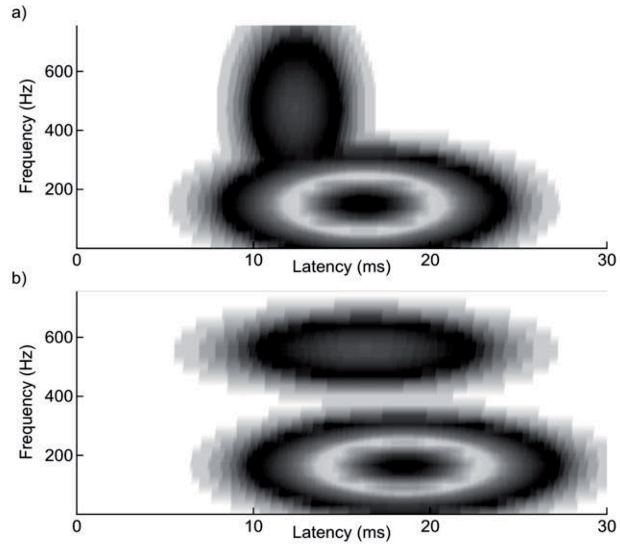

Fig. 3. Time-frequency analysis of the dataset LFC+HFO of a single volunteer using a Multichannel Matching Pursuit algorithm: a) after electric stimulation / atoms 2 and 15, and b) after magnetic stimulation / atoms 2 and 13.

For the direct comparison of the HFOs after different stimulations the channel LL4 was used, since for nine out of fourteen volunteers strong oscillations were visible in this channel. As described, the amplitude and latency of the HFOs were determined using the Hilbert-transformed signal. The mean value for the amplitude was 0.06 µV after electric stimulation. After the magnetic stimulation a smaller value of 0.04 µV was calculated (see Table III). The latencies were determined with 15.96 ms and 17.42 ms, respectively.

TABLE III
AMPLITUDE AND LATENCY OF THE HFO

		Amplitude in µV		Latency in ms	
Stimulation	Channel	Mean	SD	Mean	SD
electric	LL4	0.06	0.02	15.96	1.56
magnetic	LL4	0.04	0.01	17.42	1.17

Similar to the analysis of the LFCs, the Kolmogorov-Smirnov test confirmed the normal distribution of the data. Thus, a dependent t-test for paired samples was performed to prove the significance of the differences, again. The p-value for the amplitudes was 0.016, approving significant smaller values after the magnetic stimulation. For the latencies the p-value was 0.007 which validates the assumption of increased latencies after magnetic stimulation.

For analyzing the psycho-perceptual evaluations, the single marks were averaged. The perception of the electric stimulation on the skin was rated with 0.5. A considerably higher value of 1.4 was obtained for perception of the magnetic stimulation on the skin. Similar respective results of 0.3 and 0.9 are visible for the perception inside the tissue. In direct comparison, twelve out of the fourteen volunteers reported the magnetic stimulation to be less unpleasant.

IV. Discussion

The analysis of the N20 component after electric stimulation revealed that the results comply with the values found in literature and are within the range of inter-individual variability [2], [3], [4]. This fact indicates that the used equipment and study design were applicable.

After magnetic stimulation, the N20 component was determined in all datasets. Nevertheless, our evaluation showed significantly reduced amplitudes and significantly increased latencies after magnetic stimulation. Since the amplitude of the somatosensory evoked potential is strongly related to the amount of stimulated tissue, the results indicate that during magnetic stimulation less cells are excited. The reason for this effect could be a submaximal stimulation, meaning that not all fibers of the median nerve were activated. This could be based on the fact that the magnetic stimulation is less focal. Resulting from the larger amount of tissue which is involved during magnetic stimulation, a visible muscle contraction is already caused at a lower stimulation level. Thus, the simplified determination of the stimulation intensity by adding the motor and sensor thresholds [6] is not applicable for our magnetic stimulation technique.

Furthermore, to our knowledge, this is the first study showing the possibility of evoking HFOs superimposed to the N20 by magnetic stimulation. This was successfully demonstrated for all participating volunteers. Objective comparison of the amplitudes and latencies based on the Hilbert-transformed HFOs showed significant differences for both stimulation techniques. As already described earlier for the LFCs, the amplitudes after magnetic stimulation are significantly decreased, while the latencies are significantly increased. This complies with the assumption of submaximal stimulations.

In addition it was more difficult to find an optimal point for stimulation with the used coil. The inhomogeneity of the magnetic field cannot be excluded which could yield to varying points of stimulation at different intensities.

The time-frequency-analysis showed different characteristics for the identified atoms representing the HFOs. The decreased amplitudes after magnetic stimulation let to a reduced signal-to-noise ratio. Thus, the MMP algorithm was unable to differentiate between the two components p1 and p2 on the increasing and the decreasing flanks of the N20. In contrast only one atom with increased duration was extracted. The HFOs after electric stimulation revealed clearly separable components p1 and p2 for five out of the fourteen volunteers. However, only the HFOs on the increasing flanks of N20 were strong enough for being represented in the set of the 30 strongest analyzed atoms. All of the five volunteers were stimulated electrically first. Since the attention of the volunteers is expected to decrease with the duration of the study, this observation supports the assumption that clearly separable p1 and p2 components are visible in attentive volunteers only [9].

The psycho-perceptual evaluation showed that the magnetic stimulation was well tolerated and seems to be less unpleasant for most of the volunteers, which could be related to the submaximal stimulation using the TMS system.

V. Conclusion

We showed that LFC and HFO components related to median nerve stimulation can be evoked by both electric and magnetic stimulation. The results show that our magnetic stimulation paradigm let to submaximal activation of the median nerve. In conclusion our volunteers reported magnetic stimulation to be less unpleasant. Future work will include evaluation and subsequent definition of the necessary stimulation intensity for supramaximal stimulation.

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