ANALYSIS OF SOMATOSENSORY EVOKED POTENTIALS AFTER NON-INVASIVE ELECTROCUTANEOUS STIMULATION OF FOOT AND THIGH

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Abstract *— Following major amputations and the consequent truncation of nerves, up to 45-85% of patients are left with a neuropathic pain condition known as phantom limb pain (PLP). Recent research has shown that the addition of somatosensory feedback to daily use prostheses has the potential to alleviate the phenomenon of PLP, as long as a natural sensation, "as if" it was coming from the missing limb, is restored. One approach to evaluating how natural a sensation is perceived, is by studying the neural correlates of somatosensory stimulation, known as somatosensory evoked potentials (SEPs). Source localization techniques such as dipole modeling may be used to reconstruct the neural sources of SEPs, thus mapping the origin of each sensation within the somatosensory homunculus. Source localization of SEPs has already been demonstrated to discriminate stimulations in the upper-limb/mouth corners and between left/right side of the body, however, no evidence so far is present for the lower limb and same body side. In this work, the discriminability of SEPs relative to foot vs. thigh stimulations on the same body side is being studied. The spatiotemporal evolution of SEPs is analyzed, and preliminary source localization results are presented.*

Keywords*— Electroencephalography (EEG), somatosensory evoked potentials (SEP), source localization, dipole fitting, phantom limb pain*

Introduction

Following major amputations and consequent truncation of nerves, up to 45-85% of patients experience a chronic neuropathic pain known as phantom limb pain (PLP) [1]. Among the identified causes of PLP, there is the loss of sensory input from the missing (i.e. phantom) limb [1]. A consistent body of literature suggests that somatosensory feedback has the potential not only to improve the functional performance of prostheses [2] and to enhance the sense of embodiment [3], but also to reduce phantom limb pain [4]–[6].

Somatosensory feedback can be given through both invasive and non-invasive techniques [7], such as the (invasive) electrical stimulation of the peripheral nerves with implanted electrodes [4], [5], the (non-invasive) electrocutaneous stimulation of the sensory nerves [3], or the non-invasive mechanical stimulations such as vibrotactile stimulation on the stump [8], with the aim being, in all cases, to restore a sensation as natural as possible, as if it was coming from the missing limb.

One of the main limitations when studying somatosensory feedback is the lack of objective evaluation methods, i.e., the findings are usually indirect and mostly based upon the patients' perceptions. One opportunity for objectification may come from quantitative neurophysiological recordings such as electroencephalography (EEG), i.e., the non-invasive recording of the brain's electrophysiological activity using a set of electrodes placed on the scalp.

When a somatosensory stimulus is applied, e.g., with electrical or vibrotactile stimulation, the EEG can capture the corresponding neural response known as somatosensory evoked potential (SEP) [9]. EEG source localization techniques such as dipole modeling (as in [10]) may then be used to reconstruct the 3-dimensional sources of neural activity related to the SEP, and therefore give information on where the sensation is mapped and felt.

Being able to discriminate the stimuli at more proximal or distal areas of the same limb, would give us insights into the efficacy of a prosthesis wishing to restore a sensation from the amputated limb; by mapping indeed the stimulation with respect to the somatosensory homunculus [11], it would be possible to assess whether a realistic sensation from the missing limb is restored.

The efficacy of SEPs source localization to discriminate stimuli applied to the fingers or mouth corners, and between left and right side of the body, has already been demonstrated [12]–[14]; however, whether and to which extent it is possible to discriminate stimuli in the lower limb, and on the same side of the body, has not yet been explored.

In this work, the neural correlates and mapping of somatosensory stimuli elicited in the foot vs. thigh area of the same leg are being studied. Given the exploratory nature of the study, a cohort of healthy participants is enrolled.

Methods

Participants and experimental paradigm: Twenty healthy volunteers (ten females and ten males), aged 28.43 ± 9.7 years (mean ± std), took part in the study which was approved by the local ethical committee from Medical University Graz. All participants had right leg dominance, as assessed by the Waterloo

Footedness Questionnaire Revised test (WFQ-R) [15]. The data from one participant were excluded due to technical problems.
The experiment was organized into three blocks, of which two stimulation blocks (for the foot and the thigh area) and one final resting block.
In each stimulation block, 500 biphasic, single-pulse, square electrical current pulses of 300us were delivered every 1.5-2s, through a certified functional electrical stimulation device (Motionstim 8, Medel, Hamburg). Breaks of 3 to 4.5 seconds were inserted every four stimulations, and a fixation cross was displayed in front of the participants to avoid blinks and saccadic eye movements. The electrical stimuli were delivered through a pair of round, 3.2cm electrodes (Axelgaard Manufacturing Co., Ltd., Fallbrook, USA) applied to the skin surface (Figure 1a-b).
For the foot area, the electrodes were placed behind the malleolus, so to target the *suralis* nerve (Figure 1b-c). For the thigh area, the electrodes were placed above the knee (Figure 1a), so to target the *sciatic* nerve (Figure 1c).

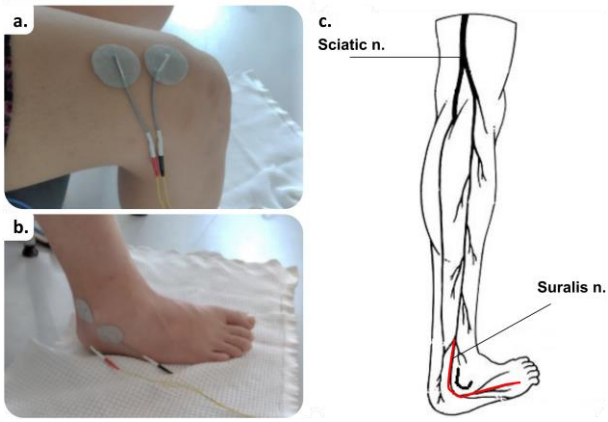

Figure1. Stimulation sites in the thigh (a) and foot (b) area, targeting the *sciatic* and *suralis* nerve (c).

The stimulation intensity was tailored to each participant, so as to elicit a clear but tolerable sensation (sensory threshold) but no muscle twitch. We defined the stimulation intensity in the foot area, and then kept the same for the thigh area. The applied current was 11.48 ± 2.58 mA (mean ± standard deviation). All stimulations were delivered on the right leg.
The order of stimulation blocks (foot or thigh) was randomized across participants. Each stimulation block lasted for approximately ~20mins, while a final resting block collected approximately 200s of resting-state EEG.

Data recording: We collected the 64 channel EEG signal at 512Hz with an eego™ sports amplifier and a waveguard™ electrode cap (ANT Neuro, Hengelo, Netherlands). Reference and ground electrodes were CPz and FPz, respectively. We digitized the exact positions of EEG electrodes with an ultrasonic position-measuring device (ELPOS, Zebris Medical GmbH, Germany).

Data analysis: We analyzed the EEG signals using Matlab (Mathworks Inc., Natick, USA) and EEGLAB (Swartz Center for Computational Neuroscience, La Jolla, USA), with a similar pipeline as in previous work from our group [10]. The raw EEG was zero-phase bandpass filtered between 0.5 and 100Hz (with a 10^{th} order Butterworth), the bad channels were interpolated, and the data were re-referenced to their common average (CAR). The continuous EEG was epoched [-0.2 0.5]s with respect to the stimulus onsets, and the trials with an abnormal probability distribution (based on standard deviation and kurtosis) were rejected. An independent component analysis (ICA) [16] was used to separate the data into components (IC) that are maximally statistically independent. The ICs were used to fit source dipoles in the brain (with the DIPFIT toolbox [17]), and only the ICs explaining more than 90% of the variance of their scalp projection, were considered for further analysis. The remaining ICs were additionally visually inspected, and the ones related to artifacts (e.g. eye movement, or electrical noise) were excluded from further analysis. Reconstruction of the signal with the so-selected IC components and mixing matrix, led us to obtain the clean EEG data. The epoched and clean data were finally split into the two stimulation conditions, i.e. foot vs. thigh stimulation.
The relevant SEP components were isolated by further epoching of the data between [0 115]ms with respect to the stimulus onset [12]–[14]. An additional ICA was finally run for each stimulation condition, and the resulting IC components were used to fit the equivalent current dipoles. All fitted dipoles were visually inspected, and the ones lying in the sensorimotor areas were identified as corresponding to the SEPs. For each participant, only one dipole for each SEP was identified. For visualization purposes, the x/y/z coordinates of the dipoles were averaged across participants. A Wilcoxon signed-rank test was used to evaluate statistical differences in the x/y/z position distributions of the foot vs thigh.
The spatiotemporal distribution of SEP components of foot vs. thigh was further inspected. A Wilcoxon rank-sum test was used to reveal statistical differences in signal amplitudes, for each electrode and time-point, between the foot and thigh stimulations. A post-hoc Bonferroni correction was applied to the significance level, to control for the type I error.

Results

Spatiotemporal evolution of SEPs:
The temporal evolution of the SEP at a selected location (Cz) is depicted in Figure 2, showing the grand-averaged amplitude of the EEG signal, in both foot and thigh stimulation conditions, with respect to the stimulus onset. Statistically significant differences between the two stimulation conditions (alpha=0.01, Bonferroni corrected) were revealed in the first [0 110]ms after stimulus onset. Within this period, both foot and thigh SEPs share the same shape (i.e.,

sequence of positive and negative deflections), but with a delay of ~10ms for the foot with respect to the thigh stimulation condition. For example, while the larger negative component peaks at ~95ms for the thigh, it peaks at ~105ms for the foot.

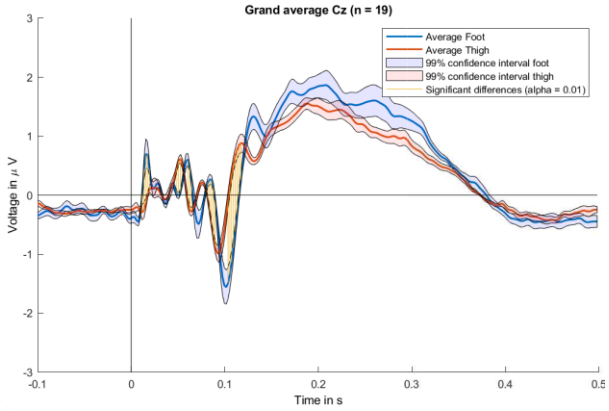

Figure 2: Grand-average amplitude of the EEG signal at location Cz, for both stimulation conditions, with respect to the stimulus onset. The variability among subjects is displayed in the confidence intervals (alpha=0.01). The time-points with statistically different SEP responses (alpha=0.01, Bonferroni corrected) are highlighted in yellow.

The spatiotemporal evolution of the SEPs for both stimulations is also displayed in Figure 3, showing the topographical representation of average scalp potential, at different time points after the stimulus onset. A small positivity at 55ms in the central electrodes, followed by a negativity at 95ms, can be seen for the thigh stimulation condition (upper row). A similar positivity at 65ms, followed by a negativity at 105ms, is visible in the foot stimulation condition (middle row). When contrasting the two conditions (lower row), it appears that the SEP components for the thigh are more frontally located than the foot.

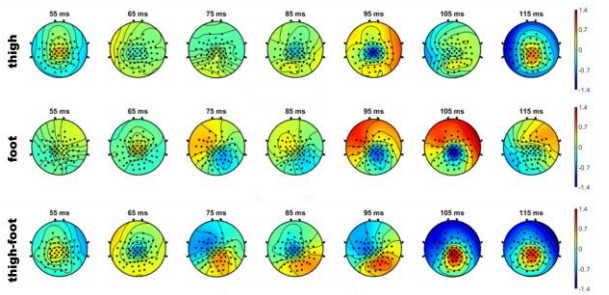

Figure 3: Topographical representations of average scalp potentials for the thigh (upper row), foot (middle row) and difference thigh-foot (lower panel), at selected time points with respect to the stimulus onset.

Source localization: The results of source localization, i.e., the estimated positions for the foot vs. thigh dipoles, averaged across participants, are depicted in Figure 4. The average difference in (x,y,z) position between foot and thigh was (-0.05, 7.8, 1.8) arbitrary units. No statistical difference in the (x,y,z) coordinates distributions between foot and thigh was found, however, a tendency (p-value = 0.08) of the foot component being located more frontally than the thigh component was highlighted.

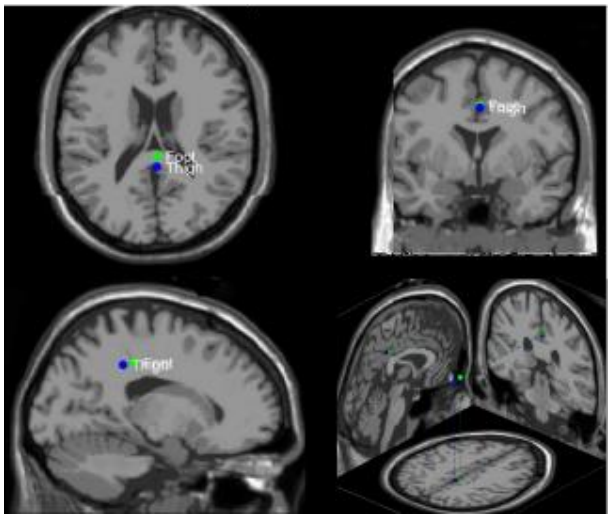

Figure 4. Estimated positions for the foot vs. thigh dipoles, averaged across participants.

Discussion

In this study, we investigated whether and to which extent the neural correlates of somatosensory stimulations applied to more proximal and distal areas of the lower limb, could be discriminated.

To do so, we analyzed the spatiotemporal evolution of somatosensory evoked potentials (SEPs) elicited by non-invasive electrocutaneous stimulation of foot vs thigh area, and additionally projected the SEPs to source space, to identify their cortical origin.

When looking at the SEPs in the time domain we could observe that, despite sharing a similar shape, the responses to stimulations in the foot vs. thigh were delayed from each other by approximately ~10ms. A delayed response coming from the foot area with respect to the thigh area can be easily explained, if considering the more distal location, and therefore longer distance to be traveled in the ascending sensory pathways, with respect to the collection point.

When looking at the spatiotemporal evolution of the SEPs, we could also find differences between foot and thigh stimulations, with the thigh SEP components being more frontally located than the foot SEP components.

When finally projecting the SEPs to source space, we could observe a tendency for the foot dipoles to be estimated more anteriorly with respect to the thigh dipoles; however, due to the dispersion of data, the difference was not significant. One approach to improve the localization of dipoles could be to increase the number of stimuli per condition. While indeed, in literature, typically 500 to 1000 stimulations are delivered [12]–[14], using only 500 stimuli per condition,

and further reducing this number when cleaning the data and rejecting artifactual trials, might not be sufficient to achieve the desired signal-to-noise. A second aspect that might have affected our recordings, is the potential presence of cross-talk between the foot and thigh stimulation condition, and so the effect of different stimulation setups could be explored in the future. As a final way to improve the reliability of source localization, the subject-specific anatomical data from MRI scans could be incorporated.

Altogether, this study could show that somatosensory stimulations even at proximal and distal locations of the same leg, produce SEPs with distinct spatiotemporal evolutions. Additional preliminary results for projecting the SEPs to source space are encouraging, however, further investigation needs to be carried out to improve the reliability of the technique.

Acknowledgments

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References

[1] D. P. Kuffler, ‘Origins of Phantom Limb Pain’, *Mol. Neurobiol.*, vol. 55, no. 1, pp. 60–69, 2018, doi: 10.1007/s12035-017-0717-x.

[2] D. Rusaw, K. Hagberg, L. Nolan, and N. Ramstrand, ‘Can vibratory feedback be used to improve postural stability in persons with transtibial limb loss?’, *J. Rehabil. Res. Dev.*, vol. 49, no. 8, pp. 1239–1254, 2012.

[3] M. R. Mulvey, H. J. Fawkner, H. E. Radford, and M. I. Johnson, ‘Perceptual embodiment of prosthetic limbs by transcutaneous electrical nerve stimulation’, *Neuromodulation Technol. Neural Interface*, vol. 15, no. 1, pp. 42–47, 2012.

[4] P. M. Rossini *et al.*, ‘Double nerve intraneural interface implant on a human amputee for robotic hand control’, *Clin. Neurophysiol.*, vol. 121, no. 5, pp. 777–783, 2010.

[5] D. W. Tan, M. A. Schiefer, M. W. Keith, J. R. Anderson, J. Tyler, and D. J. Tyler, ‘A neural interface provides long-term stable natural touch perception’, *Sci. Transl. Med.*, vol. 6, no. 257, pp. 257ra138-257ra138, 2014.

[6] C. Dietrich *et al.*, ‘Sensory feedback prosthesis reduces phantom limb pain: Proof of a principle’, *Neurosci. Lett.*, vol. 507, no. 2, pp. 97–100, Jan. 2012, doi: 10.1016/j.neulet.2011.10.068.

[7] C. Antfolk, M. D’Alonzo, B. Rosén, G. Lundborg, F. Sebelius, and C. Cipriani, ‘Sensory feedback in upper limb prosthetics’, *Expert Rev. Med. Devices*, vol. 10, no. 1, pp. 45–54, Jan. 2013, doi: 10.1586/erd.12.68.

[8] P. D. Marasco, K. Kim, J. E. Colgate, M. A. Peshkin, and T. A. Kuiken, ‘Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees’, *Brain*, vol. 134, no. 3, pp. 747–758, 2011.

[9] A. Macerollo, M. J. Brown, J. M. Kilner, and R. Chen, ‘Neurophysiological changes measured using somatosensory evoked potentials’, *Trends Neurosci.*, vol. 41, no. 5, pp. 294–310, 2018.

[10] J. Wagner, T. Solis-Escalante, P. Grieshofer, C. Neuper, G. Müller-Putz, and R. Scherer, ‘Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects’, *NeuroImage*, vol. 63, no. 3, pp. 1203–1211, Nov. 2012, doi: 10.1016/j.neuroimage.2012.08.019.

[11] W. Penfield and E. Boldrey, ‘Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation.’, *Brain J. Neurol.*, 1937.

[12] M. Schaefer, W. Mühlnickel, S. M. Grüsser, and H. Flor, ‘Reliability and Validity of Neuroelectric Source Imaging in Primary Somatosensory Cortex of Human Upper Limb Amputees’, *Brain Topogr.*, vol. 15, no. 2, pp. 95–106, Dec. 2002, doi: 10.1023/A:1021468423831.

[13] Y. Lyu, X. Guo, Z. Wang, and S. Tong, ‘Resting-state EEG network change in alpha and beta bands after upper limb amputation’, in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2016, pp. 49–52.

[14] P. Montoya *et al.*, ‘The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain’, *Eur. J. Neurosci.*, vol. 10, no. 3, pp. 1095–1102, 1998, doi: 10.1046/j.1460-9568.1998.00122.x.

[15] L. J. Elias, M. P. Bryden, and M. B. Bulman-Fleming, ‘Footedness is a better predictor than is handedness of emotional lateralization’, *Neuropsychologia*, vol. 36, no. 1, pp. 37–43, 1998.

[16] A. Delorme and S. Makeig, ‘EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis’, *J. Neurosci. Methods*, vol. 134, no. 1, pp. 9–21, Mar. 2004, doi: 10.1016/j.jneumeth.2003.10.009.

[17] A. Delorme, J. Palmer, J. Onton, R. Oostenveld, and S. Makeig, ‘Independent EEG Sources Are Dipolar’, *PLOS ONE*, vol. 7, no. 2, p. e30135, Feb. 2012, doi: 10.1371/journal.pone.0030135.