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Reproducibility of evoked and induced MEG responses to proprioceptive stimulation of the ankle joint

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ABSTRACT

Cortical processing of proprioceptive afference can be investigated by examining phase locked evoked and induced responses in cortical signals to passive movement stimuli. Reproducibility of evoked and induced responses has been studied using electroencephalography (EEG), but proprioceptive domain has received little attention. It is unclear whether evoked and induced responses to proprioceptive stimulation arising from the lower limbs are reproducible using magnetoencephalography (MEG).

Nineteen healthy volunteers (18 right-foot dominant, 36.1 ± 6.6 yr, 7 females) were measured in two MEG sessions separated by 9 ± 5 days in which their right ankle was rotated intermittently using a pneumatic movement actuator (160 stimuli, 3000 ± 250 ms interstimulus interval) to elicit evoked fields and induced responses. The peak evoked field amplitude used in the final analysis was calculated from the gradiometer pair yielding the peak vector sum over vertex (*i.e.*, the primary sensorimotor cortex for the lower limb). Peak induced response amplitudes were analyzed from the peak gradiometer demonstrating the most robust beta suppression and beta rebound. The between session reproducibility was estimated using intra-class correlation coefficient (ICC).

Evoked field amplitudes, beta suppression and beta rebound amplitudes all demonstrated a large inter-individual variation but excellent between session reproducibility (ICC >0.81). Kinematics of the proprioceptive stimuli were stable and did not correlate with MEG response strengths.

The results indicate that evoked and induced responses to proprioceptive stimuli from the lower limbs are reproducible and provide a valid tool for longitudinal experiments investigating the processing of proprioceptive afference in e.g., different clinical populations, but caution is advised when comparing individuals using these measures.

1. Introduction

Proprioceptive afference conveys information about the body position and movements to the brain (for review, see: Proske and Gandevia, 2012). Cortical processing of proprioceptive afference can be quantified in magnetoencephalography (MEG) or electroencephalography (EEG) in time domain by averaging cortical activity with respect to regular intermittent evoked (passive) movements (Alary et al., 2002; Druschky et al., 2003; Lange et al., 2001; Piitulainen et al., 2015; Smeds et al., 2016) or by quantifying coupling between movement kinematics and cortical activity during continuous movements (Bourguignon et al., 2015; Piitulainen et al., 2018b). The evoked limb movements (*i.e.*, proprioceptive stimulation) activate the proprioceptors in the muscles and joints, and the cortical EEG/MEG response (*i.e.*, evoked response) is thought to reflect primarily the processing of the proprioceptive afference. Proprioceptive origin is likely as the response is visible even when

Abbreviations: Magnetoencephalography, MEG; primary sensorimotor cortex, SM1; primary somatosensory cortex, SI; temporal spectral evolution, TSE; time-frequency representation, TFR; coefficient of variance, CoV; intraclass correlation coefficient, ICC.

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the cutaneous feedback is absent (Abbruzzese et al., 1985; Mima et al., 1996) or the level of cutaneous input is modulated during active movements (Bourguignon et al., 2015; Piitulainen et al., 2013).

In addition to evoked response, the proprioceptive stimulation induce modulations in the cortical activity at specific frequency bands, typically prominent at ~20 Hz beta band (*i.e.,* induced responses) caused by upper (Illman et al., 2020; Parkkonen et al., 2015) or lower extremity movements (Toledo et al., 2016; Walker et al., 2020). The induced response to somatosensory stimulation in the primary sensorimotor (SM1) cortex is characterized by reduction of the beta power (suppression, or event-related desynchronization) shortly after the stimulus, which is followed by delayed enhancement of the beta power (rebound, or event-related synchronization) (Parkkonen et al., 2015; Pfurtscheller and Lopes da Silva, 1999; Salmelin and Hari, 1994; Stancák and Pfurtscheller, 1995). The suppression is suggested to reflect the activation of the somatosensory processing and increased excitability of the primary somatosensory (SI) cortex, whereas the rebound is thought to reflect cortical inhibition (Neuper et al., 2006; Neuper and Pfurtscheller, 2001). The induced responses are thus potential neuronal markers in assessing functional state and dynamics of the primary sensorimotor (SM1) cortex following a disease. For example, hand function has been shown to correlate with beta rebound during recovery from stroke (Parkkonen et al., 2017).

Reproducibility of evoked and induced responses is a prerequisite for reliable estimation of proprioceptive and somatosensory functions especially in longitudinal follow-up studies. MEG is a highly reproducible method investigating brain function even in an individual level. Typically, MEG responses show large inter-individual variation but within-individual variation is low, making MEG capable of following individual brain activity over weeks or years (Boon et al., 2021; Espenhahn et al., 2017; Illman et al., 2022; Lew et al., 2021; Martín-Buro et al., 2016; McCusker et al., 2021; Piitulainen et al., 2018a). Reproducibility of the cortical evoked responses has been investigated with variety of stimulus paradigms and sensory modalities primarily using EEG. Event-related potentials have been shown to be highly reproducible in auditory (Lewis, 1984; Sandman and Patterson, 2000; Walhovd and Fjell, 2002), visual (Cassidy et al., 2012; Groves et al., 2018; Huffmeijer et al., 2014; Lewis, 1984) and cognitive domains (Cassidy et al., 2012; Sklare and Lynn, 1984; Vázquez-Marrufo et al., 2013). In the somatosensory domain, evoked EEG potentials from vibrotactile stimulation to fingers have been shown to be stable across measurement sessions (Breitwieser et al., 2012). Similarly, the evoked MEG fields to tactile stimulation are highly reproducible (Schaefer et al., 2004). Studying proprioception specifically, both MEG and EEG have been reproducible methods to quantify the cortical proprioceptive processing for hand using corticokinematic coherence approach (Piitulainen et al., 2018a, 2020). Further, Piitulainen et al. (2018a) evoked continuous 3-Hz finger movement and observed highly reproducible steady-state evoked fields in the SI cortex.

The induced responses appear reproducible irrespective of stimulus modality and frequency band of interest. Good to excellent reproducibility has been reported for frequency modulations (rebound and suppression) at alpha band to a cognitive task (Burgess and Gruzelier, 1996; Vázquez-Marrufo et al., 2017), at beta band to volitional hand movement (Espenhahn et al., 2017) and at beta band to proprioceptive or tactile stimulation of index finger (Illman et al., 2022). Further evidence for the reliability of induced responses is provided by observing the responses to ongoing oscillations (induced steady-state responses). Induced steady-state responses have been shown to be highly reliable in gamma band to visual (McCusker et al., 2021; Muthukumaraswamy et al., 2010; Tan et al., 2016), auditory (Tan et al., 2015) and somatosensory (median nerve) stimulus (McCusker et al., 2021).

The reproducibility of the evoked and induced cortical responses have been thoroughly investigated for most sensory domains, but in the somatosensory domain, majority of these studies have focused on the upper limb, and none on the lower-limb proprioception. Lower limb proprioception is of special interest because of the inherently unstable bipedal locomotion of humans and its reliance on precise proprioceptive feedback from the body and especially the lower limbs (Fitzpatrick and McCloskey, 1994). Proprioceptive information is required for a purposeful task with feedforward control (Jayasinghe et al., 2021), such as quiet standing (Gatev et al., 1999). The proprioceptors monitor the ankle joint rotations and provide a functionally crucial proprioceptive afferent feedback to the central nervous system especially from the muscle afferents of the triceps surae muscles (Berardelli et al., 1982), that are the main actuators of bipedal standing (Loram et al., 2005) and locomotion (Farris and Sawicki, 2012). Therefore, the ankle joint and the muscles controlling it are among the most important sources of lower limb proprioceptive afference for stable and efficient motor control and thus locomotion. Efficient movement execution is dependent on the processing of proprioceptive afference in the SI cortex (Richardson et al., 2016) and it has been shown that balance ability is related to cortical processing of proprioception (Goble et al., 2011; Piitulainen et al., 2018b; Walker et al., 2020).

The aim of this study was to investigate reproducibility of evoked and induced responses to proprioceptive stimulation of the ankle joint (to its evoked dorsiflexions) in healthy participants. Based on earlier findings on various sensory domains, we hypothesized that both the evoked and induced responses to lower limb proprioceptive stimulation show high reproducibility between two measurement sessions separated by ~9 days.

2. Materials and methods

2.1. Subjects

In total 23 volunteers (mean ± SD, age: 36.1 ± 6.2 yr, 8 females) were recruited for the study. The footedness was assessed with three questions: (1) with which leg would you kick a football, (2) which leg would you use in long distance jumping and (3) which leg would you lift first to step on an elevated level (such as a chair). The total number of answers for left or right was used to determine the footedness. Prior entering the study, the participants gave a written and informed consent. The study protocol was approved by the ethics committee of the University of Jyväskylä and the experiments were done in accordance to Declaration of Helsinki.

2.2. Experimental protocol

The subjects were invited to two separate measurement sessions separated by 9 ± 5 days (mean ± SD, range: 3–25 days) at the Centre for Interdisciplinary Brain Research, University of Jyväskylä. Measurements were conducted in a magnetically shielded room (Magnetical Shielding Cabin, VACOSHIELD, Vacuumschmelze GmbH & Co. KG, Hanau, Germany) where the subjects were instructed to sit relaxed in the MEG chair. Both first and the second measurement session were identical and conducted at the same time of the day. Subject's arms were resting on top of a pillow placed on their lap. Proprioceptive stimulation was induced using a MEG compatible pneumatic movement actuator (Piitulainen et al., 2018b). The participants right foot was placed on the movement actuator and position of the foot was secured in place with an elastic band. The movement actuator caused passive dorsiflexions of the ankle joint (movement range ~8°, peak angular velocity 45°/s), and after 1.5 s the ankle was returned to the initial 90° ankle joint position (Fig. 1). In both session 1 and session 2, a total 160 of intermittent ankle rotations were evoked every 3000 ms with 250 ms random jitter, totaling 8 min of data per session. The stimuli were controlled using Presentation software (version 21.1).

To block the minor auditory noise caused by the airflow in the movement actuator, the subjects wore earplugs. Any remaining noise was masked with Brownian noise played from flat panel speakers at a level at which the participants confirmed that they cannot hear any

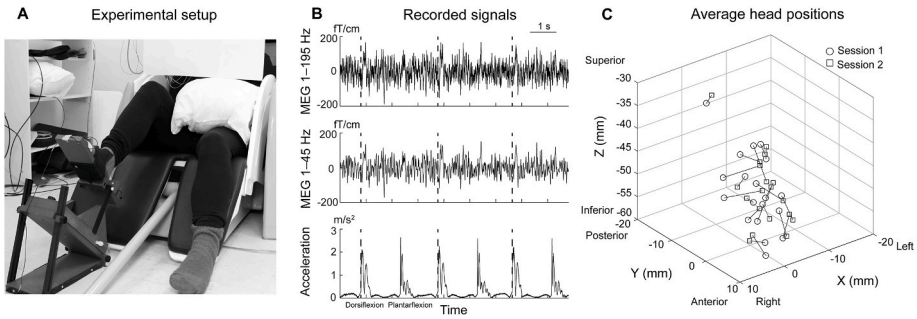

Fig. 1. Experimental setup, signals, and head position. (A) Subject's right foot attached to the pneumatic movement actuator using elastic band. (B) Continuous 1–195 Hz and 1–45 Hz MEG signal from the peak SM1 gradiometer channel, and the acceleration magnitude from a representative participant. Vertical dashed lines indicate dorsiflexion onsets. (C) 3D-average head positions between the sessions.

external noise. In addition, visual contact to the movement actuator and lower limbs were blocked with a sheet of paper to prevent visual distraction from the movement. During the measurements subjects were instructed to fixate on a marker placed in front of them on the wall of the magnetically shielded room.

2.3. MEG and kinematic measurements

MEG. MEG signals were collected using a 306-channel whole-scalp neuromagnetometer (Elekta Neuromag TRIUXTM, Elekta Oy, Helsinki, Finland). Eye blinks were recorded with electro-oculography with one electrode on the upper right corner of the right eye and the other located on the lower left corner of the left eye. Electrocardiogram was recorded using an electrode pair located below the right clavicle and below the left rib cage. Ground electrode was attached on top of the right clavicle. All signals were sampled at 1000 Hz with 0.1–330 Hz passband. Head position with respect to MEG sensors was monitored with five head-tracking coils that were attached on the subjects scalp prior measurements. Anatomical landmarks (nasion and two preauricular points), the head surface and the coils were digitized using a digitizer (Isotrak, Polhemus, Colchester, VT, USA). Continuous head position identification was used during the recording to track the subject's head position with respect to the MEG sensors.

Kinematics. Foot accelerations were recorded with a 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devies Inc. Norwood, MA, USA) attached on the first proximal phalanx of the foot. Acceleration signals were low-pass filtered at 330 Hz and sampled time-locked to MEG signals at 1000 Hz.

2.4. Data processing

2.4.1. Preprocessing of MEG signals

MEG signals were first visually inspected to identify the noisy MEG sensors, and these were given as an argument to temporally extended signal-space separation algorithm (tSSS, MaxFilter 3.0 software, Elekta Neuromag Oy, Helsinki, Finland). tSSS was run with head movement compensation to reduce the external interference and head movement effects (Taulu and Simola, 2006). Then, MEG signals were decomposed into 30 components and filtered between 1 and 40 Hz using a zero-phase finite impulse response filter (firwin in SciPy; Hamming window) using MNE Python (Gramfort et al., 2014). Noise components related to eye blinks and cardiac activity were identified based on the time-series and topographies of the independent components and were subtracted (2–3 per participant) from the data.

2.4.2. Kinematic analysis

The kinematics and evoked fields were computed using custom-made MATLAB® (MathWorks, Natick, MA, USA) scripts. First, the acceleration signals were bandpass filtered at 1–195 Hz, and Euclidian norm of the three orthogonal acceleration signals (*i.e.*, acceleration magnitude signal) was computed. Stimulus (*i.e.*, movement) onset was determined based on the acceleration magnitude onset separately for each stimulus, participant, and measurement session. Stimulus onset was determined as the timepoint where ascending limb of the acceleration magnitude reached 15% of the initial peak magnitude. Stability of the stimulus was further examined by calculating the peak slope (jerk or rate of change) of the initial ascending limb of the acceleration magnitude between 20% and 70% from the initial peak acceleration magnitude. Lastly, area under the acceleration magnitude from movement onset to 400 ms was computed to quantify the total acceleration during the dorsiflexion movement evoked by the movement actuator.

2.4.3. Evoked field analysis

MEG signals were bandpass filtered between 1 and 45 Hz and epoched from −400 to 1100 ms around the stimulus onset (*i.e.*, at 0 s). Epochs that contained signals exceeding 3 pT/cm for magnetometers or 0.7 pT/cm for gradiometers were excluded from the analysis. On average 151 ± 16 epochs for the first session and 152 ± 15 epochs for the second session were averaged to obtain the evoked field. Gradiometer signals were combined for each pair across the entire helmet by calculating their vector sum. The gradiometer pair yielding the peak vector sum over vertex (*i.e.*, the primary sensorimotor cortex for the lower limb) was used in the final analysis. The peak gradiometer pair was selected independently in each session.

2.4.4. Induced responses

Induced responses were analyzed using MNE-Python software (Gramfort et al., 2014). Beta band modulations were quantified using temporal spectral evolution (TSE) method (Salmelin and Hari, 1994). Preprocessed MEG signals were first 1–40-Hz bandpass filtered, and epoched from −0.5 s to 1.5 s with respect to the stimulus onset and the evoked responses were subtracted from the data (David et al., 2006). Average time-frequency representation (TFR) plots of the epochs were used to visually confirm the peak response gradiometer and participant's individual beta bandwidth. Then, the MEG data was filtered using the individual beta bandwidth (cut-off range from 16 ± 3 to 24 ± 3 Hz) and this bandwidth was used for both sessions within subject. Next, the signals were rectified and averaged with respect to stimulus onset and the yielded signal envelope was then used for TSE analysis. Peak gradiometer, the one that demonstrated the most robust beta suppression and rebound, was selected separately for each participant and session. If the suppression and rebound peaked on different gradiometers, the gradiometer showing the highest difference was selected. If there were no visible beta modulations in both sessions, the subject was excluded from the analysis. Exclusion of participants did not affect the results. Finally, peak amplitudes of rebound and suppression were computed. The peak values were baseline (from −100 to 0 ms) normalized with respect to the stimulus onset.

To establish reproducibility between different analysis methods in quantifying beta band modulations we further analyzed the peak

gradiometers on all frequencies from 1 to 40 Hz in steps of one Hz using Morlet wavelets and multitaper method. In wavelet analysis, the width of a wavelet was set individually for each frequency (number of cycles = frequency/2). Multitaper analysis was conducted using three tapers. Based on the resulting TFR, peak suppression (minimum) and rebound (maximum) amplitudes were computed from time window from 0 to 1200 ms for both analysis methods. Lastly, the absolute peak frequencies for suppression and rebound were computed separately from the TFR of the peak gradiometer for both Morlet wavelet and multitaper approaches.

2.5. Statistical analysis

Statistical analysis was conducted in R software (R Core Team, 2021). Normal distribution was assessed using Shapiro-Wilk test. Inter-session reproducibility of the peak acceleration magnitudes, evoked fields and induced responses were assessed using two-way mixed-effects model intraclass-correlation coefficient: ICC(3,1). ICC values of <0.4 were interpreted as poor, 0.4–0.59 as fair 0.6–0.74 as good and >0.75 as excellent reliability (Cicchetti, 1994; Piitulainen et al., 2018a). To further estimate reliability within session (between individuals) and between sessions, coefficient of variation (CoV) was calculated for acceleration parameters and evoked and induced response parameters. To examine the effect of stimulus kinematics to cortical responses, correlations between kinematic variables and evoked and induced responses were calculated.

3. Results

From the 23 recruited subjects, four were excluded from the final analyses due to technical difficulties (*e.g.*, data contaminated by artefacts and no visible evoked fields) in measurements. The remaining 19 participants (mean ± SD, 36.2 ± 6.5 yr, 7 females) were included in the movement-evoked field analysis. Three participants were excluded from the induced field analysis, as their beta band power modulations were below the noise level, resulting a sample of 16 participants (35.6 ± 6.5 yr, 5 females).

Fig. 1c shows the head position within MEG helmet between sessions for all participants. Absolute inter-session difference of the head position was only few millimeters (x-axis 1.9 ± 1.4 mm, range 0.2–4.7 mm, y-axis: 2.5 ± 2.0 mm, 0.1–5.8 mm, z-axis: 3.0 ± 2.1 mm, 0.1–7.9 mm). On average, the vector between the mean head coordinates was 5.1 ± 1.9 mm between sessions.

3.1. Kinematics of the proprioceptive stimulus

Fig. 2a shows ankle-joint kinematics between the sessions. In total 150 ± 16 and 152 ± 15 movement stimuli were included in the analysis for session 1 and session 2, respectively. The total dorsiflexion acceleration (area) demonstrated excellent reproducibility (ICC 0.78) between session 1 (364.5 ± 59.5 $m/s^2/ms$) and session 2 (366.6 ± 54.6 $m/s^2/ms$). For acceleration jerk ICC indicated good reproducibility (0.67) between session 1 (0.4 ± 0.1 m/s^3) and session 2 (0.39 ± 0.1 m/s^3). The most sensitive variable, the peak acceleration magnitude, had yielded fair reproducibility (ICC 0.48) between session 1 (2.0 ± 0.3 m/s^2) and session 2 (2.0 ± 0.2 m/s^2).

3.2. Evoked fields to the proprioceptive stimulation

The responses peaked in the same gradiometer pair between sessions for 15 out of 19 participants for the evoked field and in the remaining participants in the adjacent one. Fig. 2b summarizes the evoked field results. First panel of Fig. 2b illustrates the group averaged evoked field peaking over the somatosensory cortex at ~130 ms after stimulation onset. Inter-session reproducibility values are presented in Table 1. The evoked field amplitudes demonstrated excellent reproducibility (ICC 0.88) between session 1 (67.6 ± 25.9 fT/cm) and session 2 (66.5 ± 24.1 fT/cm). Furthermore, evoked fields did not show statistically significant correlation with any of the kinematic variables. Fig. 3 (top panel) presents the group averaged topographies of the evoked fields over the MEG sensor array. Responses peaked in gradiometer pairs above the contralateral foot region of the SM1 cortex and were of similar amplitude between the sessions.

3.3. Induced responses to the proprioceptive stimulation

In 11 out of 16 participants the beta modulation peaked in the same gradiometer, while in the remaining participants the response peak occurred in the adjacent MEG sensor. Fig. 4 summarizes the stability of induced response amplitude across the sessions. The group average of the TSE shape remained similar with beta power suppression at ~235 ms followed by rebound peaking at ~780 ms, indicating good inter-

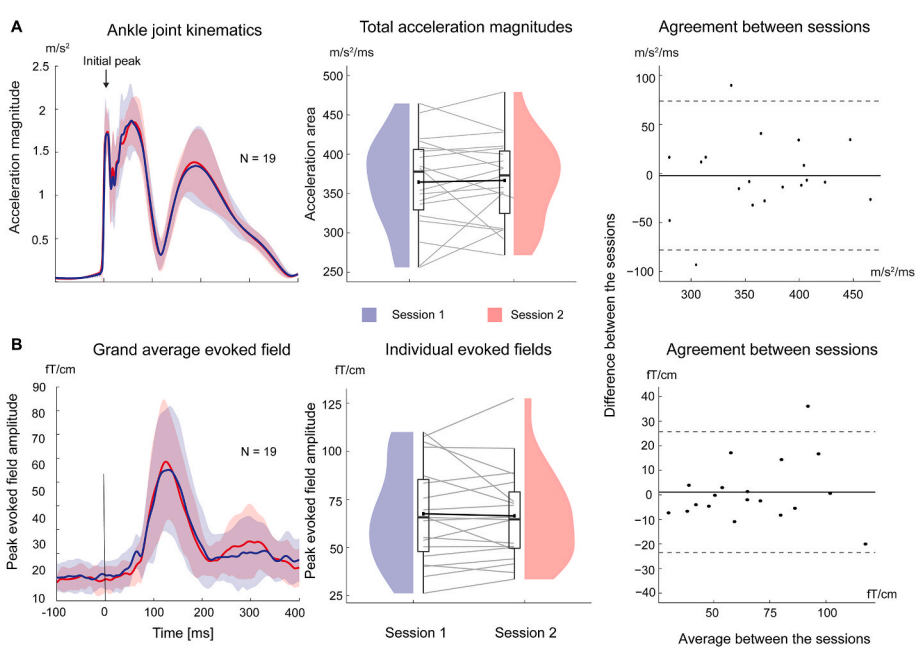

Fig. 2. Acceleration magnitude (A) and evoked fields (B) to the proprioceptive stimulation during sessions 1 and 2. Left panels show group averages with standard deviation (shaded areas). Vertical line indicates the stimulus onset. Middle panels show group (boxplots) and individual values (grey lines). In the box plots the group means relate to a black line between the sessions. Horizontal edges of the squares indicate interquartile range of the distribution, and horizontal black line indicates the median. Shaded area corresponds to the probability distribution. Right panel shows Bland-Altman plots of agreement between the sessions. Solid black lines indicate the mean difference between sessions and dashed lines correspond to 95% confidence interval.

Table 1
Inter-session reproducibility for evoked and induced responses.

	ICC
Kinematics	
Peak magnitude	0.48*
Acceleration area	0.78***
Rate of change	0.67***
MEG response	
Evoked field amplitude	0.88***
Temporal spectral evolution	
Peak suppression	0.81***
Peak rebound	0.87***
Morlet wavelets	
Peak suppression	0.87***
Peak rebound	0.91***
Multitaper	
Peak suppression	0.87***
Peak rebound	0.94***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

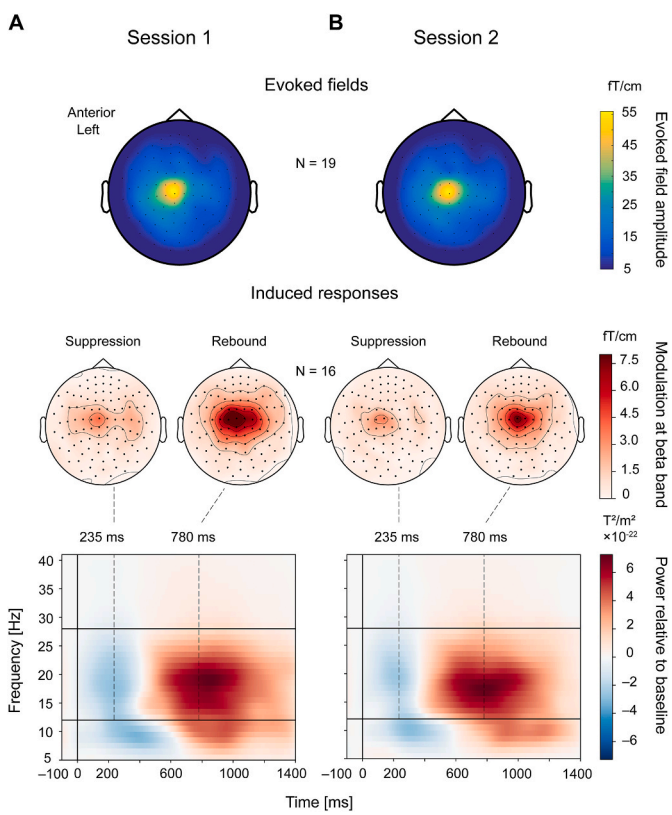

Fig. 3. Group average topography and TFR (Morlet) in (A) session 1 and (B) session 2. Top panel shows topography of the evoked field to the proprioceptive stimuli. Middle panel shows topography of TSE curve at peak suppression and rebound. Please note that beta suppression is positive because root-mean-square of the peak gradiometer pair is visualized. Bottom panel shows TFR. Horizontal black lines indicate the lower (12 Hz) and upper (28 Hz) range of the individually chosen frequency bands. Dashed lines indicate the group average timing of the peak suppression and rebound in the TSE curve with respect to the movement onset (vertical black line).

session reproducibility in the group level. However, the inter-individual variation was notable. Table 2 presents the induced response values for all analysis methods. Fig. 3 (middle panel) presents the group average topographies of the TSE responses between the sessions for the whole MEG sensor array. The topographies appear similar with slightly larger spread in session 1. Table 1 presents the ICC values. The induced response variables indicated excellent (≥0.75) inter-session reproducibility with similar ICC values between analysis methods. Group average TFR appeared the same between sessions and visualized in Fig. 3 (bottom panel). ICC indicated excellent reproducibility (ICC >0.75) for beta band baseline power for all analysis methods. Finally, the induced responses did not correlate with kinematics of the proprioceptive stimulus ($p > 0.2$).

4. Discussion

We examined the reproducibility of evoked and induced responses to proprioceptive stimuli elicited by a MEG compatible movement actuator generating passive ankle-joint dorsiflexions. Our results indicated that both evoked and induced responses to proprioceptive stimulation have excellent reproducibility, although a large inter-individual variation was observed that was especially emphasized for the induced responses. However, the individual participant's values remained stable between the different sessions separated by ~9 days. Thus, the evoked and induced responses are feasible for longitudinal experiments investigating cortical proprioceptive processing arising from the proprioceptors of the lower limbs. This result is promising for both basic research and clinical use of these proprioceptive cortical parameters. Evoked and induced fields to somatosensory stimulation are suggested as biomarkers for clinical monitoring of respective cortical functions, and to follow recovery or longitudinal alterations in various clinical conditions (Airaksinen et al., 2011; Mäkelä et al., 2015; Parkkonen et al., 2017; Vinding et al., 2019).

4.1. *Reproducibility of stimulus evoked fields*

EEG experiments have utilized event-related cortical potentials extracted from variety of experimental paradigms, stimulations, and modalities, and shown that these designs produce highly reproducible evoked potentials (Breitwieser et al., 2012; Cassidy et al., 2012; Lewis, 1984). MEG has also proven to be a highly reproducible and reliable tool investigating brain dynamics longitudinally when measurements are separated by weeks (Martín-Buro et al., 2016) or even years (Boon et al., 2021; Lew et al., 2021). In the somatosensory domain, the MEG has proven to be reproducible tool to examine proprioception (Illman et al., 2022; Piitulainen et al., 2018a) and tactile sense (Illman et al., 2022; Schaefer et al., 2004). Evoked fields to tactile stimulation (Schaefer et al., 2004) and median nerve stimulation (Solomon et al., 2015) have been used to map the SI cortex to aid *e.g.*, surgical decision making. Reproducibility to these somatosensory stimuli have been shown to be excellent in source space with millimeter differences (1–8 mm) between sessions (Schaefer et al., 2004; Solomon et al., 2015). Our sensor space analysis is well in accordance with these results as evidenced by the nearly identical topographies of the peak responses derived from the two different sessions.

We observed a marked inter-individual variation in the evoked-field amplitude with CoV of ~38% in session 1 and ~36% in session 2. However, within individuals the variation (*i.e.*, between sessions) was significantly lower with CoV being only 13%. High inter-individual variation in evoked responses can be related to the examined stimulus modality (*i.e.* proprioception) and stimulated part of the body. The primary source of the evoked response to ankle proprioception lies deep in the sulcus on the medial wall of the paracentral lobule, and thus is more challenging to detect when using MEG compared, *e.g.*, to the SM1 'hand knob' region for upper limb stimulation (Ciccarelli et al., 2005; Dobkin et al., 2004; Francis et al., 2009; Piitulainen et al., 2015). The superficial and radial currents, as well as the wall of the central sulcus in the SM1 hand region, are particularly well detected by the MEG (Hillebrand and Barnes, 2002). Therefore, part of the inter-individual variation is likely explained by their anatomical differences in lower extremity representations in their respective SI cortex.

However, the evoked responses also encode functionally relevant information. The evoked somatosensory responses have been shown to be feasible neurophysiological markers to follow stroke-recovery.

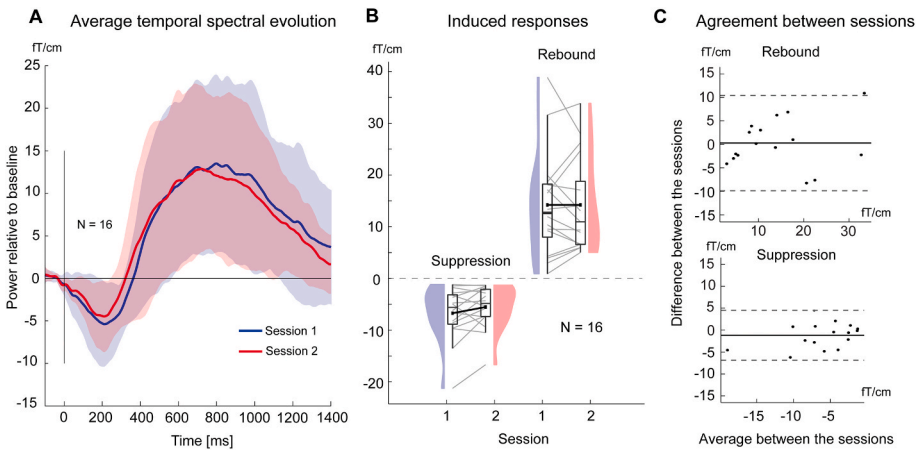

Fig. 4. Induced responses and agreement between the sessions. (A) Group average TSE for session 1 (blue) and session 2 (red). Shaded areas indicate standard deviation. Vertical line indicates the stimulus and horizontal line zero level. (B) Induced fields at group (boxplots) and individual (connected with grey lines) level for session 1 (blue) and session 2 (red). Black lines between the boxplots relate to group means. Horizontal edges of the squares indicate interquartile range of the distribution, and horizontal black line indicates the median. Shaded area corresponds to the probability distribution. Dashed line indicates zero level. (C) Bland-Altman plots of peak suppression and rebound amplitudes between the sessions. Solid black lines indicate the mean difference between sessions and dashed lines correspond to 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Peak suppression and rebound strengths, latencies, and peak frequencies (mean ± SD) between the two measurement sessions and between the three analysis methods. In addition, baseline beta power within sessions is shown.

	Session 1			Session 2		
	Temporal spectral evolution [fT/cm]	Morlet [$T^2/m^2 \times 10^{-22}$]	Multitaper [$T^2/m^2 \times 10^{-22}$]	Temporal spectral evolution [fT/cm]	Morlet [$T^2/m^2 \times 10^{-22}$]	Multitaper [T2/m2 × 10−22]
Suppression						
Relative modulation	−6.7 ± 5.2	−4.2 ± 4.6	−2.4 ± 2.2	−5.5 ± 4.2	−3.6 ± 3.4	−1.9 ± 1.6
Latency to peak [ms]	255 ± 76	350 ± 103	322 ± 77	217 ± 45	306 ± 51	291 ± 99
Peak frequency [Hz]	–	19 ± 3	20 ± 3	19 ± 3	19 ± 3	19 ± 3
Rebound						
Relative modulation	14.2 ± 10.2	11.2 ± 9.9	8.5 ± 9.0	13.9 ± 9.3	10.7 ± 10.5	7.8 ± 8.2
Latency [ms]	803 ± 116	892 ± 105	904 ± 84	760 ± 166	835 ± 165	887 ± 127
Peak frequency [Hz]	–	18 ± 3	18 ± 3	19 ± 3	18 ± 3	19 ± 3
Baseline	28.4 ± 10.1	6.5 ± 4.2	6.2 ± 4.0	27.4 ± 7.6	6.1 ± 3.1	5.8 ± 3.0

Firstly, severity of the tactile impairment in stroke is associated with reduced amplitude of the early evoked field (N20) to electrical median nerve stimulation (Forss et al., 1999). Secondly, Roiha et al. (2011) followed the recovery of behavioral hand function and evoked fields to tactile stimulation of the fingers up to three months post-stroke. The affected hand yielded weaker evoked fields compared to the unaffected hand throughout the follow-up period. However, the cortical hand representation area was significantly enlarged and was normalized back to the "healthy" size until the end of the follow-up period, and the degree of reduction in the hand representation area was correlated with improved hand function (Roiha et al., 2011). The somatosensory evoked fields can thus be utilized not only based on the response strength but also in the spatial domain to derive clinically relevant information. In proprioceptive domain concerning the upper extremity, this requires use of MEG compatible multi-finger movement actuators that has been developed by our research group (Hakonen et al., 2021). In addition, the interstimulus interval (Smeds et al., 2016) and stimulus steadiness (Mujunen et al., 2021) are known to affect the evoked field amplitude, and thus may affect the evoked response strength as well. As such, the current results encourage the use of proprioceptive stimuli in longitudinal experimental designs, especially at group level, but potentially also to follow individual patient. However, small changes in the response amplitude need to be interpreted with caution at individual level and should be confirmed optimally with several follow up recordings.

4.2. *Reproducibility of stimulus induced responses*

Reproducibility of the induced suppressions and rebounds have received some attention in cognitive domain where modulations in the alpha-band have been investigated. Alpha-band modulations to cognitive stimulation are shown to indicate good reproducibility in the group level, but the especially the peak amplitude of the modulation varies between individuals (Burgess and Gruzelier, 1996; Vázquez-Marrufo et al., 2017). Reproducibility of movement or action related beta-band modulations have received less attention. Beta modulations to active volitional wrist extension and flexion movements have demonstrated high inter-session reproducibility (Espenhahn et al., 2017). In addition, proprioceptive stimulation of the index finger has been shown to elicit highly reproducible induced fields (Illman et al., 2022). Our results are in accordance with these previous results as we also found that both peak beta suppression and rebound amplitudes have excellent reproducibility in the group level, although inter-individual variation may be substantial in the absolute response amplitudes. We also quantified the beta-power modulations using three common approaches: TSE, Morlet wavelets and multitaper method. The results demonstrated that beta modulations to proprioceptive stimulation from the lower limbs are reproducible in the group level irrespective of the analysis method used. In addition, none of the analysis methods was superior to another, thereby allowing freedom in designing the analysis pipeline in a longitudinal setting.

Inter-individual CoV of the induced response amplitudes was greater than for the evoked fields and of similar magnitude between the analysis

methods. In first session, the CoV (TSE) was ~78% (~76% in the second one) for beta suppression and ~72% (~67%) for the beta rebound. However, the inter-session CoV was much lower ~36% for beta suppression and ~25% for beta rebounds. These variations are somewhat similar to what were observed in a recent study concerning induced responses to proprioceptive stimuli of the hand (Illman et al., 2022). Differences in the cortical anatomy SI likely explain partly the inter-individual variation. The higher inter-individual variation of the induced response amplitudes, compared to evoked ones, might be partly due to its weaker response amplitude and less prominent peak, especially in the case of the long-lasting rebound. In addition, variations in circadian rhythm may affect the induced beta power modulations and therefore within-subject measurements should be conducted at the same time of the day in longitudinal studies (Wilson et al., 2014). In the current study, we controlled the between session variation due to the circadian rhythm well. The same participant was always recorded at the same time of the day. However, circadian variations may explain some of the inter-individual variation as the measurement time of the day inevitably varied between the participants. The evoked and induced responses may potentially also reflect partly different aspects of the cortical somatosensory processing, which could be one possible reason behind multifaceted modulation of the induced responses to conditioning (Barone and Rossiter, 2021).

The brain activity in a given frequency bands are hypothesized to reflect both intrinsic membrane properties of single neurons, as well as properties of the whole neuronal network involved (Neuper and Pfurtscheller, 2001). Therefore, the modulations of the brain "oscillations" provide an interesting target to probe cortical function. Parkkonen et al. (2017) utilized passive movement of the index finger to quantify the level of cortical proprioceptive processing in stroke patients. They showed that beta rebound was diminished bilaterally both in the affected and unaffected hand to the proprioceptive stimulation. During the stroke recovery, the rebound strength recovered together with behavioral hand function, although did not reach the level of healthy controls within the one-year follow-up period (Parkkonen et al., 2017). Furthermore, in healthy individuals, it has been shown that beta suppression to passive ankle joint rotations (*i.e.*, proprioceptive stimuli) correlated with standing-balance performance in young and older participants (Walker et al., 2020). Therefore, the proprioceptive stimulus induced responses seem to be clinically and functionally relevant indicators of sensorimotor behavioral and cortical function. As such, our results support the use of these measures in investigating the adaptations in cortical processing of proprioception and its connection to e.g., balance function in longitudinal experimental designs. However, some caution is suggested when individual subjects are examined. While beta suppression and rebound in the SM1 are not sensitive to slightly reduced alertness or active attention at group level, they should be maintained high to reduce individual variability (Illman et al., 2021).

4.3. Reproducibility of stimulus kinematics

As expected, the proprioceptive stimuli evoked by the movement actuator were temporally very accurate (few millisecond accuracy) and reproducible between stimuli, participants, and sessions, as previously has been demonstrated for both index finger movement (Piitulainen et al., 2015, 2018a) and ankle joint rotations (Piitulainen et al., 2018b; Walker et al., 2020). The most sensitive kinematic parameter, the peak acceleration magnitude, showed very low ~2–3% CoV between successive stimuli within individual participants, and the difference in the peak acceleration magnitude between the sessions was on average ~0.2 m/s^2 only with ~9% CoV (~7% for area, i.e., total acceleration). In addition, there was markedly lower CoV in peak acceleration magnitude within session 1 (~12%) and session 2 (~12%) compared to the respective evoked field (~38% and ~36%) or induced response amplitudes (~72–78% and ~67–~72%). Importantly, none of the kinematic parameters correlated with either evoked or induced responses. Therefore, the variability in the cortical responses were not due to proprioceptive stimulus variation. The pneumatic-movement actuators are shown to be highly feasible and reproducible tools for longitudinal investigation of the cortical proprioceptive processing both in combination with MEG and EEG (Piitulainen et al., 2018a, 2020).

4.4. Limitations

Our analysis was conducted only in the sensor level since no magnetic resonance images of the head were acquired. The head position within the MEG helmet was very similar between the recording sessions in our participants. Nevertheless, the responses peaked at different MEG sensors in some individuals between the sessions: in 5/19 participants for evoked responses and 6/16 participants for induced responses. However, the sensors were always the adjacent ones, and thus reflected the same cortical activity in both sessions. Source space analysis have shown that while the reproducibility of evoked responses to somatosensory stimuli is excellent, the location can shift a few millimeters between the sessions due to limitation in the methods (MEG noise, spatial sampling error, digitization *etc.*) and thus could cause the activity to peak in the neighboring sensor (Schaefer et al., 2004; Solomon et al., 2015). Based on our head position analysis, the differences in head position between the sessions were in the millimeter range in the current study (~5 mm difference in mean head coordinates). As such, we chose the peak response channel separately for both sessions and showed that this approach yields excellent reproducibility for both evoked and induced responses.

In the current study, the beta band modulations were absent in three participants and were excluded from the final analysis. To maximize the beta power modulation, we defined the beta band corresponding to peak modulatory activity for each participant individually, in contrast to fixed band for the entire group. The fixed beta band tends to attenuate the induced responses as the band must be wide to accommodate the inter-individual variation in the prominent beta power. In our approach, we aimed to maximize the actual individual beta band activity. Nevertheless, the applied frequency range (12–28 Hz) corresponded well with the often used fixed beta band of ~13–30 Hz (Kilavik et al., 2013). Opting this approach, we demonstrate excellent group level reproducibility for both beta suppression and rebound amplitudes to proprioceptive stimuli arising from lower limbs.

5. Conclusion

We demonstrated excellent group-level reproducibility of evoked and induced responses to proprioceptive stimulation of the ankle joint between different days of MEG recordings. As such these measures are potential tools to examine cortical processing of proprioceptive afference in longitudinal experiments. However, inter-individual variation was high, especially for the induced responses, and as thus some caution and several repeated measures are advised if the aim is to follow individual patients. To maximize MEG response strength to proprioceptive stimulation we recommend using exact, computer-controlled movement actuators to ensure consistent stimulus amplitude and timing.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Data availability statement

The data are not publicly available due to privacy or ethical restrictions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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