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RESEARCH REPORT

Attention directed to proprioceptive stimulation alters its cortical processing in the primary sensorimotor cortex

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Abstract

Movement-evoked fields to passive movements and corticokinematic coherence between limb kinematics and magnetoencephalographic signals can both be used to quantify the degree of cortical processing of proprioceptive afference. We examined in 20 young healthy volunteers whether processing of proprioceptive afference in the primary sensorimotor cortex is modulated by attention directed to the proprioceptive stimulation of the right index finger using a pneumatic-movement actuator to evoke continuous 3-Hz movement for 12 min. The participant attended either to a visual (detected change of fixation cross colour) or movement (detected missing movements) events. The attentional task alternated every 3-min. Coherence was computed between index-finger acceleration and magnetoencephalographic signals, and sustained-movement-evoked fields were averaged with respect to the movement onsets every 333 ms. Attention to the proprioceptive stimulation supressed the sensorimotor beta power (by ~12%), enhanced movement-evoked field amplitude (by ~16%) and reduced corticokinematic coherence strength (by ~9%) with respect to the visual task. Coherence peaked at the primary sensorimotor cortex contralateral to the proprioceptive stimulation. Our results indicated that early processing of proprioceptive afference in the primary sensorimotor cortex is modulated by inter-modal directed attention in healthy individuals. Therefore, possible attentional effects on corticokinematic coherence and movement-evoked fields should be considered when using them to study cortical proprioception in conditions introducing attentional variation.

KEYWORDS

magnetoencephalography, movement, muscle spindle, proprioception, selective attention, somatosensory

Abbreviations: CKC, corticokinematic coherence; DICS, dynamic imaging of coherent sources; EEG, electroencephalography; MEF, movement-evoked field; MEG, magnetoencephalography; MNI, Monteal Neurological Institute; MRI, magnetic resonance imaging; PET, positron emission tomography; SI cortex, primary somatosensory cortex; SII cortex, secondary somatosensory cortex; SM1 cortex, primary sensorimotor cortex.

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INTRODUCTION 1

Cortical processing of proprioceptive afference (i.e., from the "movement sensors," for review see (Proske & Gandevia, 2012) to the primary sensorimotor (SM1) cortex can be examined using precise computer controlled movement actuators, that is, proprioceptive stimulators, in magnetoencephalography (MEG; Alary et al., 2002; Lange et al., 2001; Piitulainen et al., 2015), electroencephalography (EEG; Desmedt & Ozaki, 1991; Mima et al., 1996; Piitulainen et al., 2020) or functional magnetic resonance imaging (MRI; Nurmi et al., 2018; Weiller et al., 1996). Corticokinematic coherence (CKC) can be used to quantify the coupling between oscillatory cortical activity measured with electrophysiological recordings (MEG or EEG) and limb kinematics (e.g., acceleration, force, etc. (Piitulainen et al., 2013a) that occurs during repetitive rhythmic voluntary or passive movements (Bourguignon et al., 2011; Jerbi et al., 2007; Piitulainen et al., 2013b). Coherence is correlation in the frequency domain between two signals, and thus, CKC peaks at the movement frequency and its harmonics, and primarily reflects proprioceptive processing in the SM1 cortex (Bourguignon et al., 2015; Piitulainen et al., 2013b). Therefore, the strength of CKC quantifies the degree of cortical proprioceptive processing and has shown to be associated with motor performance (Piitulainen, Seipäjärvi, et al., 2018b). The inter-session reproducibility of CKC is shown to be excellent at the group level (Piitulainen, Illman, et al., 2018a; Piitulainen et al., 2020). CKC is thus a potential clinical tool to detect, examine and follow deficits in cortical proprioceptive processing, for example, in newborn using EEG (Smeds et al., 2017) or in motor impairments such as Friedreich ataxia using MEG (Marty et al., 2019).

It is not known whether proprioceptive processing in the SM1 cortex is modulated by the degree of attention directed to the proprioceptive stimulation (i.e., to the movement). Attentional modulation of cortical tactile processing has been demonstrated. Attention to the tactile stimulus produce stronger cortical responses in the primary somatosensory (SI) cortex when compared to a simultaneous visual-attention task in MEG (Bardouille et al., 2010) or functional MRI (Johansen-Berg et al., 2000), or active distracting mental arithmetic tasks in positron emission tomography (PET; Meyer et al., 1991). In contrast, some MEG studies have not detected attentional modulation to somatosensory stimulation (to electrical median nerve stimulation) in the SI cortex (Mauguiere et al., 1997; Mima et al., 1998).

Our primary aim was to examine whether processing of proprioceptive afference in the SM1 cortex is modulated by inter-modal attention. The attention was directed either to visual task or to the proprioceptive stimuli (movement task)

while the right index finger was continuously moved at 3-Hz using a pneumatic-movement actuator. The attentional effect was verified by analysing alpha and beta power in the SM1 and occipital cortices. The degree of proprioceptive processing in the SM1 cortex for each task was quantified using CKC strength and sustained-movement-evoked field (MEF) amplitude. We hypothesized to observe significant attentional modulation in proprioceptive processing at the SM1 cortex when attention was shifted from one task to another. Based on the previous findings in the cutaneous tactile domain, we expected the CKC and MEFs to be stronger when the attention is directed to the proprioceptive stimulation itself.

MATERIALS AND METHODS 2

2.1 **Participants**

In total, 21 healthy adults were recruited for the study. One participant could not be scanned in MRI, and thus 20 participants were included in the final analyses (mean \pm SD age, 27.8 ± 5 years; 10 females). The mean Edinburgh handedness inventory score (Oldfield, 1971) was 76 ± 42 on the scale from -80 to 100, and 19 participants were right-handed, one ambidextrous (handedness score 20) and one was lefthanded (-80). Prior to measurements, all participants signed a written informed consent. The study conformed to the Declaration of Helsinki, and all the experiments were approved by the ethics committee of Aalto University.

2.2 **Experimental protocol**

The measurements were conducted at the MEG Core, Aalto NeuroImaging, Aalto University (Espoo, Finland) in a magnetically shielded room (Imedco AG, Hägendorf, Switzerland). Participants were instructed to sit relaxed in the MEG chair with their right hand pronated on the surface of a pneumatic-movement actuator placed on a table in front of them. For detailed description of the operating principle of the movement actuator, see (Piitulainen, Seipäjärvi, et al., 2018b). The left hand was resting on a response pad placed on their thigh. Medical tape (Leukoplast, BSN medical GMbH & Co. KG, Hamburg, Germany) was used to attach the right index finger to vertically oriented pneumatic artificial muscle (DMSP-10-100 AM-CM, Festo AG & Co, Esslingen, Germany). The actuator (Figure 1a) generated continuous flexion-extension movement (movement range 1.64 cm in the vertical direction) at the metacarpophalangeal joint of the index finger at 3 Hz (i.e., with 333 ms interstimulus interval).

To minimize the subtle auditory noise caused by the airflow in the movement actuator (Piitulainen, Seipäjärvi, **FIGURE 1** Experimental setup and visual task. (a) The participant's right-index finger was taped to the vertically moving pneumatic muscle, and an accelerometer was taped on the nail of the index finger. (b) During the *visual*-attention task the participant was identifying brief 120 ms change of fixation cross colour from black to white. During the *movement*-attention task the participant was fixated to the black fixation cross but attempted to identify missing finger movements



et al., 2018b), the participants wore earplugs, and 70 dB Brownian noise was played from flat panel speakers (Panphonics 60×60 SSHP, Tampere, Finland) on the inner wall of the magnetically shielded room. The visual contact to the moving finger was blocked with a A3-sized cardboard taped vertically to the MEG gantry. During the stimulation, the participants were instructed to fixate to a black cross (spanning 1.4 deg of visual angle) displayed on a grey background in the middle of a translucent screen.

Two separate attention tasks were used during the proprioceptive stimulation (Figure 1). During visual task, the participants were attending to the black fixation cross and attempted to detect a brief (333 ms) change of its color from black to white (visual event). During movement task, the participants were fixating their gaze to the black fixation cross but were attending to the 3-Hz-movement-stimulus sequence to detect a missing movement in it (proprioceptive event). The data from onset of the sensory event to 4 s post-event was always discarded from the data analysis. In case of perceived events, the participants responded with their left hand as fast as possible using a MEG compatible response pad. The events appeared randomly every 30 ± 10 s during the stimulation. There were 6 events for each task. Each task was performed for 6 min, and the tasks alternated in 3-min long blocks. The order of the task presentation as counterbalanced across the study group. Before start of each task, written instruction was shown in the translucent screen for 5 s, either "Focus on colour change of the fixation cross" for the visual task or "Focus on missing movements events" for the movement task. The tasks and stimuli were computer-controlled using

Presentation software (ver. 18.1, Neurobehavioral Systems, Albany, CA, United States).

2.3 | Measurements

2.3.1 | MEG

The MEG signals were recorded with a 306-channel wholescalp neuromagnetometer (Elekta NeuromagTM, Elekta Oy, Helsinki, Finland) using a passband of 0.1–330 Hz and 1kHz sampling. Electro-oculography signal was recorded with an electrode pair placed above and below the left eye to detect eye blinks and movements. The head location with respect to the MEG sensors was continuously monitored using five head-position indicator coils placed on the scalp of the participant. For this purpose, the locations of the head-position indicator coils with respect to anatomical fiducials and the head shape were first determined using an electromagnetic 3D-tracker (Isotrak, Polhemus, Colchester, VT, USA).

2.3.2 | MRI

Anatomical MRI images were acquired using a 3-tesla MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) and a 32-channel receiving head coli at the Advanced Magnetic Imaging centre of Aalto University. MRI data were measured with a high-resolution T1-weighted Magnetization Prepared Rapid Gradient Echo pulse sequence (repetition time = 2,530 ms, echo time = 3.3 ms, flip angle = 7, 256 x 256 matrix, 176 sagittal slices, 1-mm resolution).

2.3.3 **Kinematics**

Acceleration of the index finger was recorded with a 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devies Inc. Norwood, MA, USA) attached on the nail of the right index finger. Acceleration signals were low-pass filtered at 330 Hz and sampled at 1 kHz time-locked to the MEG signals.

2.4 **Data processing**

2.4.1Preprocessing

Continuous MEG data were first preprocessed off-line using the oversampled temporal projection (Larson & Taulu, 2018) algorithm to reduce uncorrelated sensor noise. Then, temporal signal space separation with head movement compensation was applied to suppress external interferences (MaxFilter 2.2 software, Elekta Neuromag Oy, Helsinki, Finland, Taulu & Simola, 2006). Noisy MEG sensors identified based on visual inspection of the raw data were given as an argument both to the oversampled temporal projection and the temporal signal space separation algorithms.

Independent components related to eye-blinks and heartbeats were removed from the MEG data. To this end, the data were decomposed into 30 independent components using fast independent component analysis algorithm (Hyvärinen, 1999) as implemented in the MNE-Python software version 0.17.0 (Gramfort et al., 2013). For independent component analysis, the data was filtered between 1-40 Hz using a zero-phase finite impulse response filter (firwin in SciPy 1.2.1; Hamming window). The components related to eye-blinks and heartbeats were confirmed by visual inspection of time-series and topographies and, thereafter, were subtracted from the data.

2.4.2Coherence analysis

Coherence analysis was conducted on the sensor level, but the CKC results at the 3-Hz movement frequency were confirmed also at the source level (please, see Source level coherence analysis and visualization below). The continuous data were split into 2-s epochs with a 1.6-s epoch overlap, leading to a frequency resolution of 0.5 Hz (Bortel & Sovka, 2007). Epochs with magnetometer signals of >3

pT/cm and gradiometer signals of >0.7 pT were excluded from the analysis to avoid contamination by muscle activity or external MEG artifacts. Next, the coherence analysis (Halliday et al., 1995) was performed yielding cross-, power and coherence spectra as well as cross-correlograms between MEG signals and Euclidian norm of the three orthogonal accelerometer signals. Each epoch of acceleration was normalized by its Euclidian norm prior the coherence analysis. A single optimal coherence value was estimated per gradiometer pair as done previously (Bourguignon et al., 2015). Briefly, the coherence was computed in the optimal direction within the two-dimensional space spanned by the gradiometer pair.

After the coherence analysis, the gradiometer pair showing the peak CKC value at the coherence spectrum at 3 Hz (i.e., at the movement frequency) among 20 preselected Rolandic gradiometer pairs contralateral to the movement was identified, and was used to quantify the CKC strength separately at 3 Hz and its first harmonic at 6 Hz. This was done separately for each participant, and the selected gradiometer pair was always the same in both tasks (visual and movement). Topographic distributions of CKC were visualized using Fieldtrip software (Oostenveld et al., 2011).

2.4.3 Source level coherence analysis and visualization

The dynamic imaging of coherent sources (DICS) beamformer (Bourguignon et al., 2013; Gross et al., 2001) was used to estimate CKC between MEG signals and Euclidian norm of the accelerometer signals in the source space. To this end, a forward model was first created. The forward model creation requires co-registration of MEG sensor positions and MRI data as well as creation of the source space, and boundary element model surfaces. First, cortical surfaces were reconstructed from T1 images with FreeSurfer's recon-all algorithm (Freesurfer software v. 6.0, Fischl et al., 1999). Thereafter, FreeSurfer's watershed algorithm was used to create a single-compartment boundary element model of the inner scull. Second, each participant's MEG sensor positions were co-registered with MRI data by manually identifying and marking fiducial points (i.e., nasion, left and right preauricular points). The fiducials and digitized scalp points (~100) were aligned with the participants' scalp through translations and rotations using an automated co-registration of the coreg function in the MNE-Python software package (Gramfort et al., 2013). Thereafter, the alignment was adjusted manually. Third, a volumetric source space was created using a grid of candidate dipoles with a 5-mm spacing between the dipoles. The leadfield with three components was reduced to the leadfield with two components corresponding to the highest singular values. The noise covariance matrix was estimated from the file for which the source space CKC was computed.

Finally, CKC maps were created at the 3-Hz movement frequency by computing CKC for all sources using DICS algorithm. The resulting CKC maps were transformed into Monteal Neurological Institute (MNI) template brain, and the CKC peak values and their locations were determined by searching the local maxima from the CKC maps. The MNI coordinates of the CKC peaks were averaged across the participants, and the resulting grand average MNI location was plotted on the template brain.

2.4.4 | Movement-evoked fields

MEG signals were averaged with respect to the movement onsets of the finger extensions occurring every 333 ms to quantify peak amplitude of the sustained MEF vectorsums of the gradiometer pairs for *visual* and *movement* task separately, that is, the strength of cortical activity related to the continuous 3-Hz movement. The MEFs were filtered through 1–65 Hz, and the peak amplitude was defined both (1) for the same gradiometer pair that showed the peak CKC value at 3-Hz above the SM1 cortex and (2) for the gradiometer pair showing the peak sustained field amplitude above the SM1 cortex because the peak MEF was not always on the same pair as the peak CKC within each participant.

2.4.5 | Power analysis

To confirm the effectiveness of the attentional modulation, MEG power at alpha (7–14 Hz) and beta (15–29 Hz) bands were quantified for the same gradiometer pair that showed the peak CKC value at 3-Hz (*i.e.*, above the SM1 cortex) and at alpha (7–14 Hz) band for mean of two gradiometer pairs over the left and right occipital cortices. The power analysis was otherwise identical to the coherence analysis, but a flattop-weighted window was used to allow power comparisons across the participants.

2.5 | Statistical analysis

The statistical analyses were performed in IBM SPSS Statistics software (ver. 26). Shapiro-Wilk test was used to confirm the normal distribution of the data. Paired-samples T-test was used to compare the CKC strength, MEF amplitudes, alpha and beta MEG power, and reaction time between visual- and movement-attention tasks, and Pearson correlation coefficient was computed between the tasks to estimate the consistency of the CKC strength.

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3 | RESULTS

Proprioceptive stimulation was successful for all participants with 784 \pm 30 epochs of MEG data per task (mean \pm *SD*; range 681–813) accepted to the CKC analysis (~2% of the epochs were rejected). Equal number of MEG data epochs was used for both tasks within each participant.

The participants maintained their attention well during the tasks, missing on average only 0.3 ± 0.7 visual events (out of 6) and 0.25 ± 0.7 movement events. In general, the participants only missed a single visual or movement event here and there, but most of the participants (15 out of 20) identified all the events. The reaction times did not differ significantly between the tasks (*visual* 556 ± 176 ms versus *movement* 572 ± 157 ms, p = .383, t = 0.894).

3.1 | Corticokinematic coherence (CKC)

Figure 2 shows coherence spectra and grand-averagetopographic distributions of CKC in the sensors level and source location in the source space for visual and movement attentional tasks. In all participants and tasks, CKC analysis yielded strong CKC in sensor (range 0.24–0.89; value of 1 corresponds to maximally coherent signals) and source (0.22–0.62) space peaking at the 3-Hz-movement frequency and its harmonics. As expected, CKC peaked at the contralateral (left) Rolandic SM1 cortex.

Figure 3 shows mean and individual CKC strength values for both conditions. The source space analysis revealed that CKC strength at the 3-Hz movement frequency was significantly (p = .007, t = 3.00) weaker when the attention was directed to the proprioceptive stimulus (0.40 ± 0.09) than when the attention was directed out from the proprioceptive stimulus during the *visual* (0.43 ± 0.10) task. However, at the sensor level, the difference in CKC strength between the *visual* (0.58 ± 0.16) and *movement* (0.56 ± 0.17) tasks did not reach statistical significance at the 3-Hz movement frequency (p = .083, t = 1.83), or its first 6-Hz-harmonic frequency (*visual* 0.45 ± 0.20 versus. *movement* 0.43 ± 0.19 , p = .362, t = 0.94).

Strong positive correlation was observed in CKC strength between visual and movement tasks (sensor level: r = 0.943, p < .001, source level: r = 0.827, p < .001, Figure 3). The CKC strength was weaker in 16 out of 20 (in sensor level) or 17 out of 20 (in source space) participants during the *movement* task when compared to the *visual* task. In general, the CKC strength remained stable between the task for most of the participants, and significantly lower



FIGURE 2 Coherence spectra, grand-average-topographic distributions and cortical source location of the CKC during visual- and movementattention tasks. (a) Corticokinematic coherence peaked at movement frequency (3-Hz) and its harmonics. Gray lines indicate individual spectra and black solid lines indicate the group-mean spectrum. (b) CKC peaked at the gradiometer pairs over the left Rolandic SM1 cortex contralateral to the right-hand-proprioceptive stimulation. Grand-average-topographic distribution at 3 Hz is shown. (c) Grand-average peak source location for CKC superimposed to MNI template brain. The source location and MNI coordinates are given in red for visual and blue for movement task



FIGURE 3 Corticokinematic coherence (CKC) during visual- and movement-attention tasks in sensor (a) and source (b) levels. Boxplots in the left panels present group mean of CKC. Error bars indicate range. Horizontal line indicates median. X is the mean. Horizontal boundaries of the boxes indicate quartiles. Middle panels show individual CKC values for visual- and movement-attention tasks. Each line presents a participant. Scatterplots in the right panels indicate correlation of CKC value between visual- and movement-attention tasks

values were detected for source space when compared to sensor level CKC (visual: p < .001, t = 6.08; movement: p < .001, t = 5.20). The data were normally distributed (Shapiro-Wilk, p = .735 - 0.924).

3.2 Movement-evoked field (MEF) amplitudes

Figure 4 shows peak MEF amplitude for the peak CKC and MEF gradiometer pairs separately, and related grand-averagetopographic distributions during visual and movement tasks. The peak CKC gradiometer pair was most often different than the peak MEF one (visual: 14 out of 20, movement: 13 out 20), but always a gradiometer just adjacent to it. That is, the most prominent MEF response did not solely explain the CKC response, and thus we reported the MEF values for both peak CKC and peak MEF sensors separately. The topographic distributions of the peak MEF response (Figure 4c) clearly show the enhanced SM1 cortex response when directing attention to the proprioceptive stimulation.

The MEF response to proprioceptive stimulus was significantly stronger (p = .019, t = 2.57) when the attention was directed towards it during the *movement* $(31.2 \pm 11.6 \text{ fT/cm})$



FIGURE 4 Peak amplitude of sustained-movement evoked fields (MEF) during visual- and movement-attention tasks in the gradiometer pair showing the peak MEF (a) and CKC (b) response, and topographic distributions of peak MEF amplitude and difference between the tasks (c). Boxplots present group means of MEF. Error bars indicate range. Horizontal line indicates median. X is the mean. Horizontal boundaries of the boxes indicate quartiles. Right panel in A shows individual peak MEF values for visual- and movementattention tasks. Each line presents a participant

FIGURE 5 Grand-average power spectra and topographic distributions of the alpha and beta power between the visual- and movement-attention tasks. (a) Grand-average power spectra for the same gradiometer pair that showed the peak CKC value above the SM1 cortex (left panel) and for mean of the two gradiometer pairs showing highest alpha power above the occipital (visual) cortex (right panel). Between task differences are indicated by the p-values for the alpha and beta bands respectively (highlighted in grey colour). (b) Difference between movement and visual task MEG power across all gradiometer pairs for alpha (left panel) and beta (right panel) bands. Visual task values were always subtracted from the movement task values

task when compared to situation when the attention was directed away from it during the *visual* (26.9 \pm 7.8 fT/cm) task (Figure 4a,c). The MEF response in the CKC gradiometer pair did not differ significantly (p = .131, t = 1.58) between the *movement* (27.0 \pm 10.5 fT/cm) and *visual* (24.6 \pm 6.9 fT/ cm) tasks (Figure 4b).

3.3 | MEG power at SM1 and occipital cortices

Figure 5 shows MEG power spectra at SM1 and occipital (visual) cortices during the *movement* and *visual* attentional tasks, and difference in the grand-average-topographic power

distribution in alpha and beta bands between the tasks. The beta power was significantly weaker (p = .008, t = 2.93) during the *movement* task in the gradiometers above SM1 cortex, and similarly the alpha power was weaker during the *visual* task (p = .017, t = 2.62) in the gradiometers above the visual cortex, both indicating modality specific shift in attention. The alpha power difference in the SM1 cortex was nonsignificant (p = .105, t = 1.70).

4 | DISCUSSION

We examined whether processing of proprioceptive afference is modulated by inter-modal directed attention using an MEG-compatible movement actuator to stimulate the proprioceptors of the hand, and CKC and MEFs to quantify the consequent proprioceptive processing in the SM1 cortex. Our results indicated that the cortical processing of proprioceptive afference was significantly modulated by the change in the degree of attention to the proprioceptive stimulus, accompanied with significant attentional modulation observed in the SM1 cortex beta power. Attention to the proprioceptive stimulation supressed the sensorimotor beta power (by ~12%), enhanced movement-evoked field amplitude (by ~16%) and reduced corticokinematic coherence strength (by \sim 9%) with respect to attention directed to the *visual* task. These results demonstrate that attentional effects should be taken in account when quantifying the cortical proprioceptive processing using CKC or MEFs in healthy individuals, and potentially even more so in conditions and populations with attentional variation or deficits, for example, in prolonged recordings, clinical populations, children or longitudinal studies.

Our results in the proprioceptive domain are in line with the previously demonstrated attentional modulation of evoked responses in the tactile domain. Attention to the tactile stimulus has shown to evoke stronger cortical responses in the SI cortex when compared to simultaneous visual-attention task in functional MRI (Johansen-Berg et al., 2000) or active distracting mental arithmetic tasks in PET (Meyer et al., 1991). In MEG, only induced responses (beta modulation/rebound) have shown to be increased with attention to tactile stimulation (Bardouille et al., 2010), but the attentional modulation has not always been detected in evoked responses to electrical median nerve stimulation in the SI cortex using MEG (Mauguiere et al., 1997; Mima et al., 1998). These contradictory findings could potentially be explained with the different population of the somatosensory afferents activated when using cutaneous tactile versus electrical median nerve stimulation. While tactile stimulation activates primarily the cutaneous (tactile) mechanoreceptors, the electrical stimulation activates a mixture of cutaneous and muscle (proprioceptive) afferents, especially the wide diameter axons, including type -WILEY

Ia-afferents from the muscle spindles. Another difference is that median nerve stimulation induces strong response in the SM1 cortex. If the primary response is strong, it can partly mask the weaker cortical activity related to the attentional modulation. The proprioceptive stimulation strongly activated the SM1 cortex which may partly explain why we did not detect significant attentional modulation in the sensor level CKC, but the source space analysis using DICS seemed to alleviate this problem which led also to clearly lower interindividual variation in CKC strength.

It is also noteworthy that CKC was clearly weaker at source than sensor level. One would expect the opposite effect as the beamformer is expected to enhance the signal-to-noise ratio, and thus CKC strength, by supressing the sensor noise and contributions from cortical areas beyond the SM1 cortex. It is hard to draw a conclusion for this issue from the current data, but it may be possible that the beamformer supress part of the genuine physiological signal driving the coherence between the hand kinematics and cortical activity. This may occur because the cortical response signal to proprioceptive stimulation is strong and widespread in MEG, and thus partly correlated across the different cortical source points. Future work should be directed to clarify this issue mathematically with verifications on simulated and physiological MEG data, especially in the context of CKC and other designs utilizing coherence analysis.

For MEFs, the attention directed to the proprioceptive stimulation significantly enhanced the response amplitude already at the sensor level, being in line with previously shown enhancement amplitude of steady-state potentials to vibrotactile stimulation of the skin at flutter range (~20 Hz) when attention was directed to the stimulated index finger (Giabbiconi et al., 2004; Pang & Mueller, 2014). Surprisingly, the modulation direction in MEF was opposite to CKC. It is hard to draw a conclusion why the directed attention to and out from the proprioceptive stimulation would attenuate the CKC and enhance MEF, and vice versa, other than that the associated neuronal populations involved in these coherence and amplitude based variables may partly differ. Stronger responses improve MEG signal-to-noise ratio which could be expected to strengthen the coherence (Muthukumaraswamy & Singh, 2011). However, the peak CKC gradiometer pair was most often the adjacent (i.e., different) one to the peak MEF gradiometer pair. This means that both the CKC and MEF peaked close to each other at the hand SM1 cortex, but the associated neuronal populations were partly different. This further suggests that CKC reflects partly different proportion of the cortical proprioceptive processing than the MEFs. The CKC strength is primarily dependent on phase coupling between the limb kinematic and cortical signals, but amplitude coupling may also affect the CKC strength. On simulated signals, the coherence strength is -WILEY- EIN European Journal of Neuroscience

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positively associated with the signal-to-noise ratio, but only in noisy signals (Muthukumaraswamy & Singh, 2011). The MEG signal can be considered "noisy" due to unavoidable continuous physiological "brain noise." Nevertheless, this relationship is not straight forward in physiological data. In the current data and population, the CKC strength and sustained MEF amplitude were not significantly correlated (r < 0.073, p > .759). However, CKC strength has previously been shown to be positively correlated with the sustained MEF amplitude (Piitulainen, Illman, et al. 2018a), but not always (Piitulainen, Seipäjärvi, et al., 2018b). The reason for this weak and variable relationship is most likely in the highly variable shape of the sustained MEF between individuals. The sustained MEF typically contains several peaks, most likely because of severely overlapping proprioceptive neuronal processing at different spatiotemporal dynamics during the fast repetitive stimulation (occurring every 333 ms in the current study) including both extension and flexion phases of the movement. Nevertheless, the most prominent MEF peak was always clearly localized in the same or adjacent gradiometer pair as the CKC peak, indicating close spatial and functional relationship of the respective neuronal populations.

Drevets et al., (1995) suggested that selective attention to tactile stimulus of the fingers enhances the cortical response because of generalized active suppression of background activity in other somatosensory regions. They demonstrated this pattern of cortical activity using PET to anticipated stimuli. The sensorimotor beta power was indeed supressed when the attention was directed to the movement (proprioceptive) task in the current study, which is in line with prior observations from MEG studies demonstrating suppression of alpha and beta power in the SM1 cortex prior anticipated or expected tactile stimulus or task of the hand (van Ede et al., 2011, 2017; Jones et al., 2010). These studies utilized a more event-related design compared to the current design, and thus enabled quantification of power fluctuations prior the expected event, and thus are not perfectly analogous design to the current continuous 3-Hz proprioceptive stimulation design which activates the SM1 cortex in sustained manner. However, the attentional effect was detectable even the SM1 cortex was continuously active confirming that our participants effectively shifted their attention away from the proprioceptive stimulation during the visual task.

The cortical processing of proprioception may differ from tactile processing. For example, we have previously shown that CKC reflects cortical proprioceptive processing with negligible contribution from cutaneous tactile afference (Bourguignon et al., 2015; Piitulainen et al., 2013b). Most of cortical proprioceptive processing occurs unconsciously. The proprioception reaches our attention (active perception) only when something unexpected happens in our movement, for example, when an object is heavier than our brain predicted. However, the tactile sense is used in more active conscious manner, for example, to explore shape and surface objects. As proprioception only seldom reach our attention, it could be expected that the early cortical proprioceptive processing in the SM1 cortex would be highly responsive to active attention, as our MEF and CKC results indicated. We really need to focus intensively to perceive or imagine our movements. One example comes from mental training of skilled athletes which requires high concentration and practice to accomplish demanding motor imaginary tasks. However, further studies are needed to confirm these hypotheses in specific attentional designs.

In addition, tactile and proprioceptive modalities are processed in different cortical regions and thus local neuronal networks. Tactile input is directed mainly to areas 1 and 3b of the SI cortex (Kaas, 1983), whereas areas 3a and 2 receive proprioceptive input (from joint and muscle receptors) and respond to joint movements (Burchfiel & Duffy, 1972; Schwarz et al., 1973) as well as to passive stretching of muscles (Lucier et al., 1975). The human primary motor (M1) cortex also receives fast proprioceptive feedback during both active and passive hand movements while it remains silent during tactile stimulation (Goldring & Ratcheson, 1972). Therefore, the earliest and primary cortical proprioceptive input is processed in the SM1 cortex, which is the main generator of CKC (Piitulainen et al., 2013b). It is also noteworthy that the cerebellum appears to have a strong role in the unconscious proprioceptive processing via the fast dorsal spinocerebellar tract (Bosco & Poppele, 2001). Together, these functional and anatomical differences between proprioceptive and tactile cortical processing may also explain their different attentional modulation when examined with MEG. However, future studies are needed to directly compare their modulatory differences.

Our results were focused to the SM1 cortex, but secondary somatosensory (SII) cortex has been more responsive to attentional modulation than SI cortex when median nerve stimulation has been applied in MEG (Mauguiere et al., 1997; Mima et al., 1998). Mima et al., (1998) used oddball paradigm with median nerve stimulation at 2 Hz. Their design was very similar to the currently evoked movements at 3 Hz. Therefore, it could be expected that the proprioceptive response in the SII cortex could have been modulated even more by attention than in the SM1 or SI cortex. We attempted but could not quantify the SII cortex CKC response. The SM1 cortex CKC response is very strong and thus spreads widely to other MEG sensors. However, attentional modulation (by mental counting of the median nerve stimuli) in the SII cortex appears to be significant only with long (21.6 s versus 2.4 s) inter-stimulus intervals (Mauguiere et al., 1997). Electrophysiological

experiments in monkeys have shown that 80% of the SII cortex neurons modulated (58% increased) their activity with selective attention to tactile stimulus, but "only" 50% of the SI cortex neurons modulated (all increased) their activity (Hsiao et al., 1993). In addition, the SI and SI cortices seem to have partially different functional roles in the sensation of flutter at 5–50 Hz during vibrotactile stimulation of the skin (Salinas et al., 2000). All the aforementioned findings underline the functional differences between SM1/SI and SII cortices.

The SI cortex is thought to processes low level stimulus features, whereas the SII cortex appears to be higher in "hierarchy" of sensorimotor integration, and thus is involved, e.g., in retention of relevant features of the afference in the working memory (for a review, see Pleger & Villringer, 2013) and via ventral somatosensory pathway to long-term memory and learning (Friedman et al., 1986). Therefore, it could be that stronger attentional modulation in the SII cortex may be related to working memory processes or other more prolonged sensorimotor processes that may not be well detectable when using CKC with rapid stimulation rate in MEG. Our results suggest that selective attention has effect on proprioceptive processing in the SM1 cortex, but it also serves in important feedforward role to transmit the pre-processed proprioceptive information to higher-order cortical regions that may then be further modulated by the selective attention.

It is noteworthy that our results should be compared and replicated in populations with severe attentional deficits, such as stroke patients, prior applying CKC method to investigate clinical populations. Our observations were demonstrated only in healthy young individuals. These results are important for potential future clinical studies using CKC or MEFs to quantify the early cortical proprioceptive processing in SM1 cortex. It is also noteworthy that attentional modulation may have stronger or otherwise different effect to proprioceptive processing in the SM1 cortex during active tasks compared to passive proprioceptive stimulation. This may be the case especially during highly skilful motor actions requiring conscious proprioceptive attention, for example, to hand position and trajectory in dart competition. In everyday actions proprioception processing is mainly unconscious and reaches attention only during unexpected events, and thus the role of attention is likely less pronounced compared toother sensory modalities. However, future studies could be advised to attempt to examine the effect of attention on cortical proprioceptive processing also during more naturalistic highly skilled active tasks. In addition, attentional load and task demands in the current tasks were relatively low, and thus our participants most likely mainly relayed on a bottom-up capture strategy of the sensory event (or its absence during movement task) rather than a strategy of active top-down EIN European Journal of Neuroscience FENS

monitoring of the sensory input Therefore, the future studies could further examine whether a more demanding attentional task would modulate even more the proprioceptive processing in the SM1 cortex.

5 | CONCLUSIONS

The processing of proprioceptive afference in the SM1 cortex was significantly modulated by the inter-modal directed attention to the proprioceptive stimulus, accompanied with significant attentional modulation of sensorimotor beta power. Therefore, attentional effects should be considered when CKC or MEFs are used to study cortical proprioception in conditions that potentially introduce attentional variation, for example, due to repeated or lengthy sessions and clinical condition such as stroke. However, further studies are needed to compare healthy individuals to populations with impaired sustained attention or maintenance of alertness. These results also suggest that the SM1 cortex has potentially a role in attentional modulation of the proprioceptive afference, and a feedforward role of preprocessing and passing the crucial proprioceptive information to other important cortical regions involved in motor control and learning.

PATIENT CONSENT STATEMENT

Prior to measurements, all participants signed a written informed consent.

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CONFLICTS OF INTEREST

No conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors significantly contributed to this work. HP and TN contributed to conception and design, data acquisition and statistical analysis. TN involved in participant recruitment. HP and MH contributed to MEG analysis. HP contributed to

writing of the first draft and acquiring funding. HP, TN and MH contributed to writing – review and editing.

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ETHICS APPROVAL

The study conformed to the Declaration of Helsinki and all the experiments were approved by the ethics committee of Aalto University.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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