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RESEARCH ARTICLE

Sensory Processing

Corticokinematic coherence is stronger to regular than irregular proprioceptive stimulation of the hand

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Abstract

Proprioceptive afference can be investigated using corticokinematic coherence (CKC), which indicates coupling between limb kinematics and cortical activity. CKC has been quantified using proprioceptive stimulation (movement actuators) with fixed interstimulus interval (ISI). However, it is unclear how regularity of the stimulus sequence (jitter) affects CKC strength. Eighteen healthy volunteers (16 right-handed, 27.8 ± 5.0 yr, 7 females) participated in magnetoencephalography (MEG) session in which their right index finger was continuously moved at ~3 Hz with Constant 333 ms ISI or with 20% Jitter (ISI 333 ± 66 ms) using a pneumatic-movement actuator. Three minutes of data per condition were collected. Finger kinematics were recorded with a three-axis accelerometer. CKC strength was defined as the peak coherence value in the Rolandic MEG gradiometer pair contralateral to the movement at 3 Hz. Both conditions resulted in significant coherence peaking in the gradiometers over the primary sensorimotor cortex. Constant stimulation yielded stronger CKC at 3 Hz (0.78 ± 0.11 vs. 0.66 ± 0.13, $P < 0.001$) and its first harmonic (0.60 ± 0.19 vs. 0.27 ± 0.11, $P < 0.001$) than irregular stimulation. Similarly, the respective sustained-movement evoked field was also stronger for constant stimulation. The results emphasize the importance of temporal stability of the proprioceptive stimulation sequence when quantifying CKC strength. The weaker CKC during irregular stimulation can be explained with temporal and thus spectral scattering of the paired peripheral and cortical events beyond the mean stimulation frequency. This impairs the signal-to-noise ratio of respective MEG signal and thus CKC strength. When accurately estimating and following changes in CKC strength, we suggest using precise movement actuators with constant stimulation sequence.

NEW & NOTEWORTHY Cortical proprioceptive processing can be investigated using corticokinematic coherence (CKC). The findings show that CKC method is sensitive to temporal stability in the stimulation sequence. Although both regular and irregular sequences resulted in robust coherence, the regular stimulation sequence with pneumatic movement actuator is recommended to maximize coherence strength and reproducibility to allow better comparability between groups or populations.

jitter; kinematics; movement-evoked field; proprioception; somatosensory

INTRODUCTION

Proprioceptive afference to the primary sensorimotor (SM1) cortex can be quantified in magnetoencephalography (MEG) or electroencephalography (EEG) either using cortical evoked responses to regular intermittent passive movements (1–4) or computing coupling between movement kinematics and cortical activity (using MEG or EEG) during continuous movements, i.e., corticokinematic coherence (CKC) (5, 6). Kinematics of limb movements have shown to be coherent

with cortical activity during continuous voluntary (5, 7, 8) and passive (3, 7, 9, 10) movements. CKC can be quantified using any signal picking the rhythmicity of the movement (acceleration, force, electromyography, etc.) (11) and peaks at fundamental frequency (i.e., stimulation frequency) and at its harmonics (3, 5). CKC primarily reflects proprioceptive processing in SM1 cortex with negligible influence of tactile afference (7, 12). Apparent latency of CKC is 50–100 ms (12) corresponding to the timing of the strongest deflection in the cortical movement-evoked field to voluntary (13) and



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passive movements (3). Therefore, it is likely that the neural basis of CKC and movement-evoked fields are closely related. CKC strength is feasible and reproducible variable to be used in longitudinal studies in MEG (9) and EEG (14). In addition, CKC can be used clinically to quantify deficits in proprioceptive processing in newborns using EEG (15) or motor impairments such as Friedreich ataxia using MEG (16).

Coherence is correlation of two signals in frequency domain ranging from 0 (i.e., no correlation at a given frequency) to 1 (i.e., perfect correlation). Strength of coherence depends on both amplitude and phase coupling between the signals of interest (17, 18). The phase coupling is required for nonzero coherence between the two signals, whereas amplitude coupling can further increase the strength of the coherence (19), especially in the case of low signal-to-noise ratio (SNR) (20), that is typical in MEG and EEG recordings. As the phase coupling is in a key role for coherence strength, the temporal stability of the voluntary or evoked movements is expected to be the primary factor determining the strength of CKC. Previous research has shown that CKC strength and cortical representation did not differ between movements at different rates both for voluntary (~1, ~2, ~3 Hz) (21) and passive (3, 6, and 12 Hz) (3) movements. However, as phase coupling is mainly dependent on the conduction velocity, it is expected to remain constant during stimulation. Therefore, experimental manipulation to improve the SNR, and thus amplitude coupling, should lead to greater CKC strength (20).

Currently, it is unknown how movement stability affects CKC strength. Our primary aim was to examine whether CKC strength is dependent on the temporal regularity of the passive-evoked-movement sequence, i.e., the stability of the proprioceptive stimulation. We expected that CKC strength is stronger for regular than irregular stimulation as regular stimulation sequence would enhance the SNR of the cortical response strength thereby improving the amplitude coupling and ultimately strengthen the CKC when compared with irregular stimulation. The improved SNR would be reflected in the MEG power spectrum in favor of regular stimulation condition. However, anticipation of a very regular (1-ms accuracy in interstimulus interval, ISI) stimulus sequence attenuates the amplitude of the cortical response to the stimulus (22, 23) and thus could hinder CKC strength. As such, irregular stimulus sequence could potentially enhance both the amplitude of the cortical response to the stimulus and CKC strength. Therefore, we explored the interaction of ISI and cortical response field and hypothesized that the sustained-movement fields would be stronger for irregular than constant stimulation because anticipation of regular stimulation has shown to attenuate the response amplitude in the other somatosensory domains (24, 25). Optimizing proprioceptive stimulation is especially important for clinical applications of CKC method, such as functional localization of cortical hand representation (5) or quantifying cortical proprioceptive processing in patient groups (15, 16), because optimization will both improve the accuracy and reduce the recording time needed for robust cortical estimates.

MATERIALS AND METHODS

Subjects

In total, 21 healthy adults (means \pm SD age, 27.8 \pm 4.9 yr; 10 females) were recruited for the study. Of the 21 participants, 19 were right-handed, one ambidextrous, and one was left-handed. The mean Edinburgh handedness inventory score (26) was 77.14 \pm 41.37 on the scale from -80 to 100. Prior to measurements, all the 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.

Experimental Protocol

The measurements were conducted at the MEG Core, Aalto NeuroImaging, Aalto University (Espoo, Finland) in a magnetically shielded room (Imedco AG, Hagendorf, Switzerland). Subjects were instructed to sit relaxed in the MEG chair with their right hand pronated on the surface of a pneumatic-movement actuator (see details from Ref. 3), placed on a table in front of them (Fig. 1A). The left hand was resting on their thigh. Medical tape (Leukoplast, BSN medical GmbH & Co. KG, Hamburg, Germany) was used to attach the right index finger in place on top of the vertically oriented pneumatic artificial muscle (DMSP-10-100 AM-CM, Festo AG & Co, Esslingen, Germany). The actuator induced continuous extension-flexion movement at metacarpophalangeal joint of the index finger. To minimize the auditory noise caused by the airflow in the movement actuator, the subjects wore earplugs, and 70 dB Brownian noise was played from flat panel speakers inside the magnetically shielded room. In addition, to prevent visual distraction from the movement, the subjects were instructed to watch a landscape video. The visual field was partly blocked with a sheet of paper to hide the movement actuator.

Two movement conditions with or without jitter were used. Constant condition consisted of a continuous movement at 3 Hz (fixed ISI 333 ms). Jitter condition consisted of a similar continuous movement sequence, but with a random 333 \pm 66 ms (\pm 20% jitter) ISI. The mean ISI was 333 ms. The same stimulus sequences were used for all participants. The recordings were done in six 1-min blocks (180 stimulus in each), alternating between the two conditions. Each condition was repeated three times (in total 6 min of data). Initiating condition was counterbalanced across the participants. The stimuli were computer-controlled using NeuroMag software.

Measurements

MEG.

Prior to entering shielded room, all the participants were asked to remove any metallic objects they were wearing and were provided with nonmagnetic clothing. The MEG signals were recorded with a 306-channel whole scalp neuromagnetometer (Elekta Neuromag, Elekta Oy, Helsinki, Finland). The signals were sampled at 1 kHz with passband of 0.1–330 Hz. Eye blinks were recorded with electro-oculography by an electrode pair located above and below the left eye. Location of the head with respect to the MEG sensors was monitored with five head-position indicator coils. The coils,

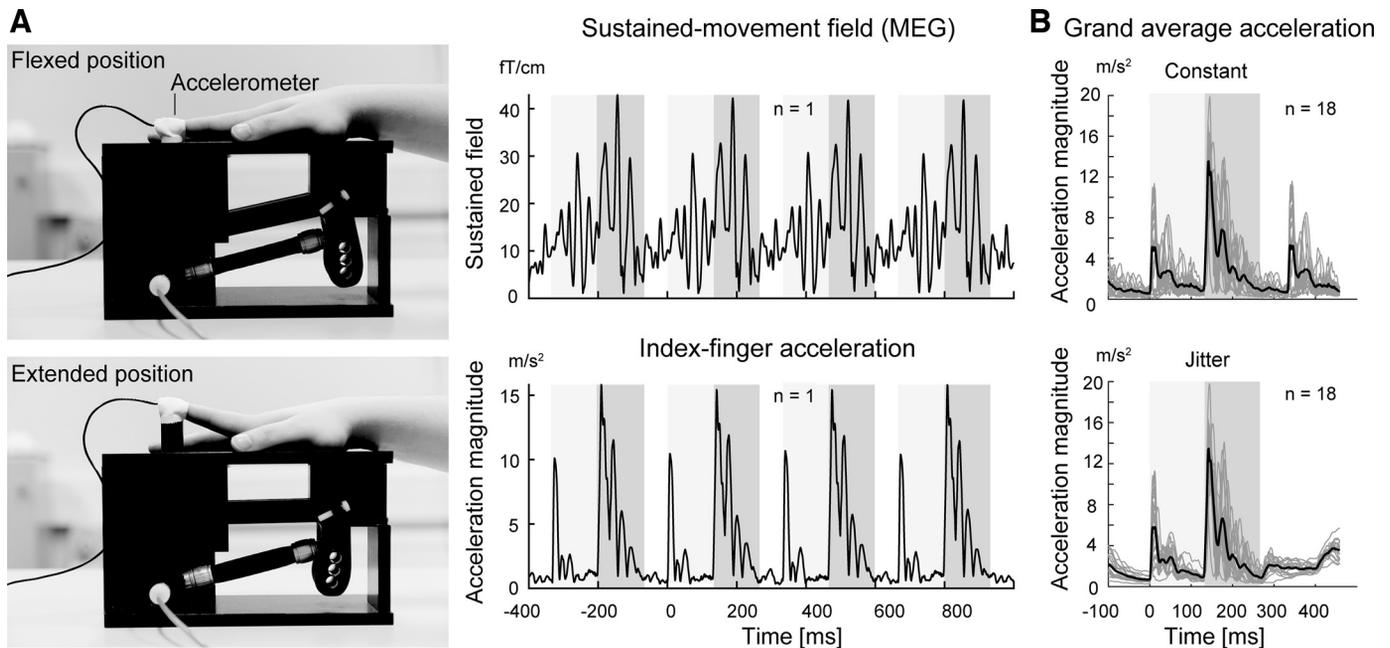


Figure 1. Experimental design and signals. *A*: pneumatic movement actuator, averaged sustained-movement field of the most responsive magnetoencephalography (MEG) gradiometer pair contralateral to the stimulated hand and acceleration magnitude during constant stimulation of a representative participant. Four movement cycles are shown. *B*: grand average (black) and individual (gray) acceleration magnitudes in Constant and Jitter conditions. Finger extension phase is highlighted in light gray and flexion phase with dark gray color.

anatomical landmarks (nasion and two preauricular points), and head surface were digitized to the same coordinate system using a three-dimensional (3-D) digitizer (Isotrak, Polhemus, Colchester, VT). During the recording, the subject's head position with respect to the MEG sensors was tracked by continuous head position identification.

Kinematics.

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

Data Processing

Preprocessing of MEG signals.

First, the signals were visually investigated to identify noisy MEG sensors. From each participant, on average 2–3 noisy sensors were identified. Then, denoising of the MEG signals was performed using oversampled temporal projection (OTP) (27) algorithm to reduce uncorrelated sensor noise. After OTP, temporally extended signal-space separation algorithm (tSSS, MaxFilter 2.2 software, Elekta Neuromag Oy, Helsinki, Finland) was applied with head movement compensation to suppress external interference and effect of the head movement. Noisy MEG sensors based on visual inspection were given as an argument both to the OTP and tSSS algorithms, and an automatic noisy MEG sensor detection (autobad option) was used in tSSS to identify unnoticed additional noisy channels.

MNE Python software (28) was used to remove noise components of eyeblinks and heartbeats from the MEG data. The MEG data were decomposed into 30 components using fast

independent component analysis (ICA) algorithm. For ICA, the data were filtered between 1 and 40 Hz using a zero-phase finite impulse response filter (firwin in SciPy; Hamming window). The noise components were confirmed by visual inspection of time-series and topographies, and were subtracted from the final data.

Coherence analysis.

Coherence analysis was conducted on sensor level. The continuous data were split into 4-s epochs with 3.2-s epoch overlap, leading to frequency resolution of 0.25 Hz (29). Epochs with magnetometer signals of >3 pT/cm, and gradiometer signals of >0.7 pT/cm were excluded from the analysis. Next, coherence analysis (30) that yielded cross-, power, and coherence spectra and cross-correlograms was computed between MEG signals and Euclidean norm of the three orthogonal accelerometer signals (i.e., acceleration magnitude). Each epoch of acceleration was normalized by its Euclidean norm prior to coherence analysis. The number of included epochs for coherence analysis was fixed for both conditions according to the condition that had lower number of epochs during analysis.

Coherence was estimated for each gradiometer pair as done by Bourguignon et al. (12). Briefly, the coherence was computed in the optimal direction within the two-dimensional space spanned by the gradiometer pair. Then, gradiometer pair showing the peak CKC value among 20 preselected gradiometer pairs contralateral to the movement above the Rolandic hand region was identified. This procedure was repeated for each participant, condition (Constant and Jitter), and frequency of interest (3-Hz stimulation frequency and its first harmonic at 6 Hz). If the gradiometer pair differed between the conditions, the pair showing

stronger mean CKC across the two conditions was selected for the final analysis. Topographic distributions of CKC were visualized using Fieldtrip software (31).

Sustained-movement fields and MEG signal power.

Sustained-movement field amplitude and MEG signal power were quantified to test whether regularity of the proprioceptive stimulation affects the MEG response strength that could enhance the coherent MEG-response SNR and thus CKC strength. First, MEG signals and Euclidean norm of acceleration signals (i.e., acceleration magnitude) were averaged with respect to trigger onsets of the evoked movements for each participant separately. Then, the sustained-movement-evoked fields were filtered with passband of 1–95 Hz and acceleration magnitude with passband of 1–195 Hz. Finally, amplitude of the most prominent peak of sustained-movement-evoked field (sustained-movement fields) was quantified for the same gradiometer pair that showed the peak CKC value, separately of the extension and flexion phase of the movement. MEG power was estimated in the same gradiometer pair where the CKC peaked at 3 Hz. Power spectra were obtained from the coherence analysis.

Finger kinematics.

Regularity of the movement stimuli was estimated from the Euclidean norm of the three orthogonal acceleration signals, i.e., from the acceleration magnitude signal. Euclidean norm is not sensitive to accelerometer orientation and thus removes a major source of variability. Acceleration peak magnitudes were calculated for both extension and flexion direction between the conditions. In addition, mean acceleration was quantified as integral of the acceleration magnitude during the entire movement cycle of the stimulus (0–266 ms from movement onset including both extension and flexion peaks). Variability in the acceleration peaks in extension direction was quantified by calculating the coefficient of variance between the peaks. Stability of the movement onset was quantified by calculating the slope of the extension acceleration peak for both conditions.

Statistical Analysis

Statistical analysis was conducted in R software (32). Normal distribution was ensured with Shapiro–Wilk test. Pearson correlation was used to examine possible associations between CKC strength, MEG power, peak sustained-movement field amplitude, and finger kinematics.

Statistical significance of coherence.

The statistical significance of participants' individual coherence levels was analyzed according to Halliday et al. (30) and Bourguignon et al. (5). The analysis was carried under the hypothesis of linear independence of Fourier coefficients from epoch to epoch at each frequency of interest while also taking into account the use of overlapping epochs. Alpha level was set to $0.05/(N_f \times N_s)$ to correct for multiple comparisons. $N_f = 2$ for the number of tested frequencies (stimulation frequency and its first harmonic) and $N_s = 20$, the number of gradiometers included.

CKC, sustained-movement fields, and signal power.

A one-way repeated-measures multivariate analysis of variance (MANOVA) was used to compare CKC strength on the frequencies of interest (stimulation frequency, 3 Hz and first harmonic frequency, 6 Hz) between the conditions (Constant and Jitter). Similar statistical approach was taken on peak sustained-movement field amplitudes for extension and flexion direction. MANOVA was used to compare both MEG and acceleration signal power on the frequencies of interest between the conditions. Paired t test was used as post hoc test and Bonferroni correction was used for multiple comparisons.

Finger kinematics.

To quantify the proprioceptive stimulus, paired t tests were used to compare acceleration peak magnitudes for extension and flexion direction, the integral of the acceleration across the whole movement cycle (across both extension and flexion phases), and the slope of acceleration at extension onset (jerk) between Constant and Jitter conditions.

RESULTS

Due to technical problems in the recordings, three subjects were excluded from the final analyses that were performed for 18 (16 right-handed, 27.8 ± 5.0 yr, 7 females, Edinburgh handedness inventory score 75.55 ± 44.26) participants. The number of epochs was fixed to be the same in both conditions for each participant separately (means \pm SD 201 ± 10 epochs, range 181–201). The number of rejected epochs was on average 5 ± 8 .

Corticokinematic Coherence and Kinematics

Figure 2A shows coherence spectra for the constant and jitter proprioceptive stimulation conditions, respectively. The coherence peak scatters to wider range of frequencies in the Jitter condition, which is visible especially at the first harmonic. The coherence strength reached the significance level ($P < 0.05$) for all participants in Constant and Jitter conditions at both frequencies, with one exception at the first harmonic frequency (i.e., 6 Hz) during Jitter condition.

Figure 2B presents CKC strength at the individual and group levels. In all participants, CKC was stronger for Constant than Jitter condition. Statistically significant effect was found between the conditions ($F_{2,16} = 91.31$, $P < 0.001$). CKC was stronger in Constant (0.78 ± 0.11) than in Jitter condition (0.66 ± 0.13) at stimulation frequency ($t_{17} = 8.38$, $P < 0.001$). Similarly, CKC was stronger in Constant (0.60 ± 0.19) than in Jitter (0.27 ± 0.11) at first harmonic ($t_{17} = 12.26$, $P < 0.001$). Within-condition comparisons of CKC strength between 3 Hz and 6 Hz showed that CKC strength was weaker at first harmonic than at stimulation frequency in both Constant ($t_{17} = 3.69$, $P < 0.01$) and Jitter ($t_{17} = 8.77$, $P < 0.001$) conditions.

Figure 1B shows kinematics of the proprioceptive stimulation for both conditions. Peak acceleration magnitude in extension direction had a significant difference ($t_{17} = -3.78$, $P = 0.0015$) between Constant (8.16 ± 1.8 m/s²) and Jitter (9.27 ± 1.83 m/s²) conditions. However, there were no statistically significant differences in peak acceleration magnitudes ($t_{17} = -0.03$, $P = 0.975$) between Constant (15.18 ± 2.29 m/s²)

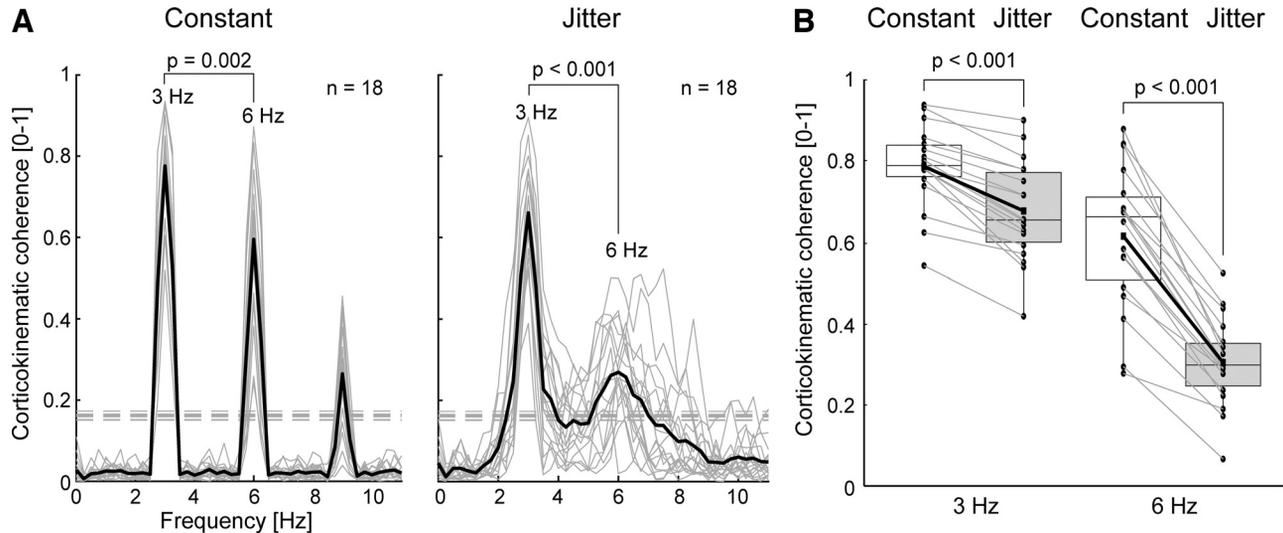


Figure 2. Coherence spectra and peak corticokinematic coherence (CKC) strength. **A:** coherence spectra for Constant and Jitter conditions. Dashed lines indicate the participant's thresholds ($P < 0.05$) for significant coherence. **B:** strength of CKC at the group (boxplots) and individual (black dots) levels for Constant (white) and Jitter (light gray) conditions. The group mean CKC values are connected with black lines between the conditions, and individual values with gray lines. Horizontal edges of the squares indicate interquartile range of the distribution, and horizontal black line indicates the median.

and Jitter ($15.18 \pm 2.19 \text{ m/s}^2$) conditions in flexion direction. Acceleration magnitudes for the whole movement cycle were well replicated between the conditions with no differences between the Constant ($0.82 \pm 0.24 \text{ m/s}^2/\text{ms}$) and Jitter ($0.83 \pm 0.23 \text{ m/s}^2/\text{ms}$) conditions ($t_{17} = -1.783$, $P = 0.09$). In the beginning of the movement cycle, initial finger extension peak magnitude was stable in Constant condition (coefficient of variation $4.7 \pm 3.3\%$) but in Jitter condition had more variation (coefficient of variation $26.9 \pm 6.1\%$). The slope of the averaged ascending limb of finger extension acceleration (jerk) was similar ($t_{17} = 1.5$, $P = 0.152$) in Constant ($1.37 \pm 0.8 \text{ m/s}^3$) and Jitter ($1.27 \pm 0.8 \text{ m/s}^3$) conditions. The acceleration magnitude neither correlated with CKC strength at stimulation frequency in Constant ($r = 0.095$, $P = 0.71$) or Jitter ($r = 0.0073$, $P = 0.98$) conditions, nor at first harmonic in Constant ($r = 0.360$, $P = 0.145$) or Jitter ($r = 0.330$, $P = 0.187$) conditions.

Figure 3 presents topographic distribution of CKC for both conditions at the stimulation frequency and its first harmonic. As expected, CKC peaked at the gradiometer pairs over the left Rolandic SM1 cortex contralateral to the proprioceptive stimulation. The spatial pattern was similar across conditions and frequencies, but the CKC was weaker in Jitter condition, and especially for the first harmonic of the stimulation frequency.

MEG and Acceleration Power at Frequencies of Interest

Figure 4 shows MEG power spectra during Constant and Jitter conditions and its association with CKC strength at 3-Hz stimulation frequency. MEG and acceleration signal power were weaker in Jitter condition. Significant difference was found for MEG power between the conditions ($F_{2,16} = 14.97$, $P < 0.001$). MEG power at stimulation frequency was significantly greater ($t_{17} = 4.76$, $P < 0.001$) in Constant condition ($649.9 \pm 446.2 \text{ fT/cm}^2/\text{Hz}$) compared with Jitter condition ($415.6 \pm 248.4 \text{ fT/cm}^2/\text{Hz}$). Similarly, MEG power was significantly greater ($t_{17} = 3.82$, $P = 0.0014$) at first harmonic

frequency in Constant condition ($374.9 \pm 274.6 \text{ fT/cm}^2/\text{Hz}$) compared with Jitter ($174.5 \pm 98.1 \text{ fT/cm}^2/\text{Hz}$). MEG power at stimulation frequency and CKC strength had a significant positive correlation (Fig. 4C) in both Constant ($r = 0.60$, $P = 0.008$) and Jitter conditions ($r = 0.56$, $P = 0.016$).

For acceleration signal power, significant difference was found ($F_{2,16} = 149.81$, $P < 0.001$) between the conditions. Acceleration signal power was significantly greater at stimulation frequency ($t_{17} = 17.1$, $P < 0.001$) in Constant condition ($27.96 \pm 5.45 \text{ ms}^{-2}/\text{Hz}^{-1/2}$) compared with Jitter condition ($14.79 \pm 4.18 \text{ ms}^{-2}/\text{Hz}^{-1/2}$). Acceleration signal power was also significantly greater ($t_{17} = 10.2$, $P < 0.001$) at first harmonic in Constant condition ($28.09 \pm 11.64 \text{ ms}^{-2}/\text{Hz}^{-1/2}$) compared with Jitter condition ($5.36 \pm 2.27 \text{ ms}^{-2}/\text{Hz}^{-1/2}$). Acceleration signal was not associated (Fig. 4D) with CKC strength in either Constant ($r = -0.22$, $P = 0.39$) or Jitter conditions ($r = -0.21$, $P = 0.39$).

Sustained-Movement Fields

Figure 5A illustrates the grand averages of sustained-movement fields for Constant and Jitter conditions. The most prominent peak was observed in flexion direction of the stimulus. Significant main effect was found between the stimulation conditions ($F_{2,16} = 9.26$, $P = 0.0021$) and peak ($F_{1,17} = 21.84$, $P < 0.001$). The sustained-movement field peak amplitude at extension phase was stronger ($t_{17} = 3.27$, $P = 0.005$) in Constant ($34.69 \pm 14.22 \text{ fT/cm}$) than in Jitter ($26.72 \pm 12.79 \text{ fT/cm}$) condition. Similarly, sustained-movement field peak amplitude at flexion phase (at $\sim 190 \text{ ms}$) was stronger ($t_{17} = 3.44$, $P = 0.003$) in Constant ($44.96 \pm 17.95 \text{ fT/cm}$) than in Jitter ($39.28 \pm 16.84 \text{ fT/cm}$) condition.

CKC strength and sustained-movement field amplitudes were significantly associated at the 3-Hz stimulation frequency (Fig. 5B). For finger extension phase, significant correlation was observed only in Jitter ($r = 0.50$, $P = 0.034$) but not in Constant ($r = 0.44$, $P = 0.064$) condition. For

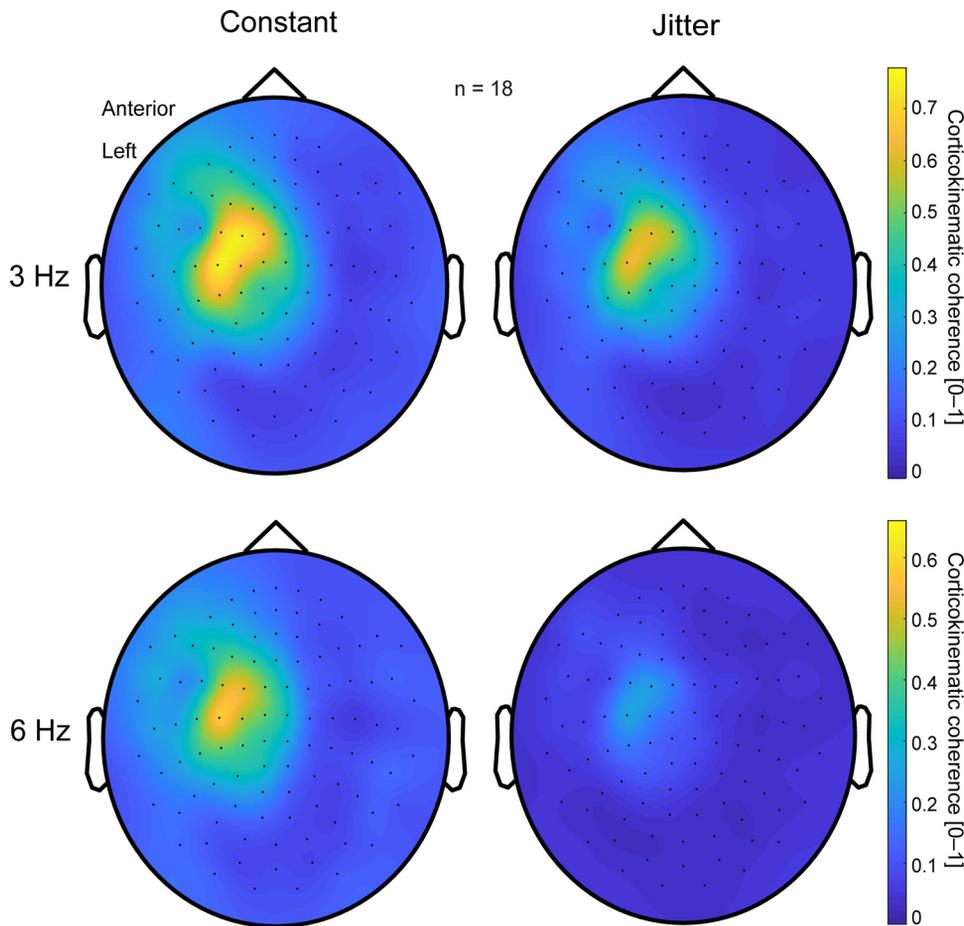


Figure 3. Grand-average topographic distributions of corticokinematic coherence (CKC) ($n=18$) at stimulation frequency (*top*) and its first harmonic (*bottom*) during Constant and Jitter conditions. Please note that the color scales vary between the frequencies.

finger flexion phase, the CKC strength correlated positively with sustained-movement field amplitude in both Jitter ($r=0.64$, $P=0.004$) and Constant ($r=0.50$, $P=0.035$) conditions.

DISCUSSION

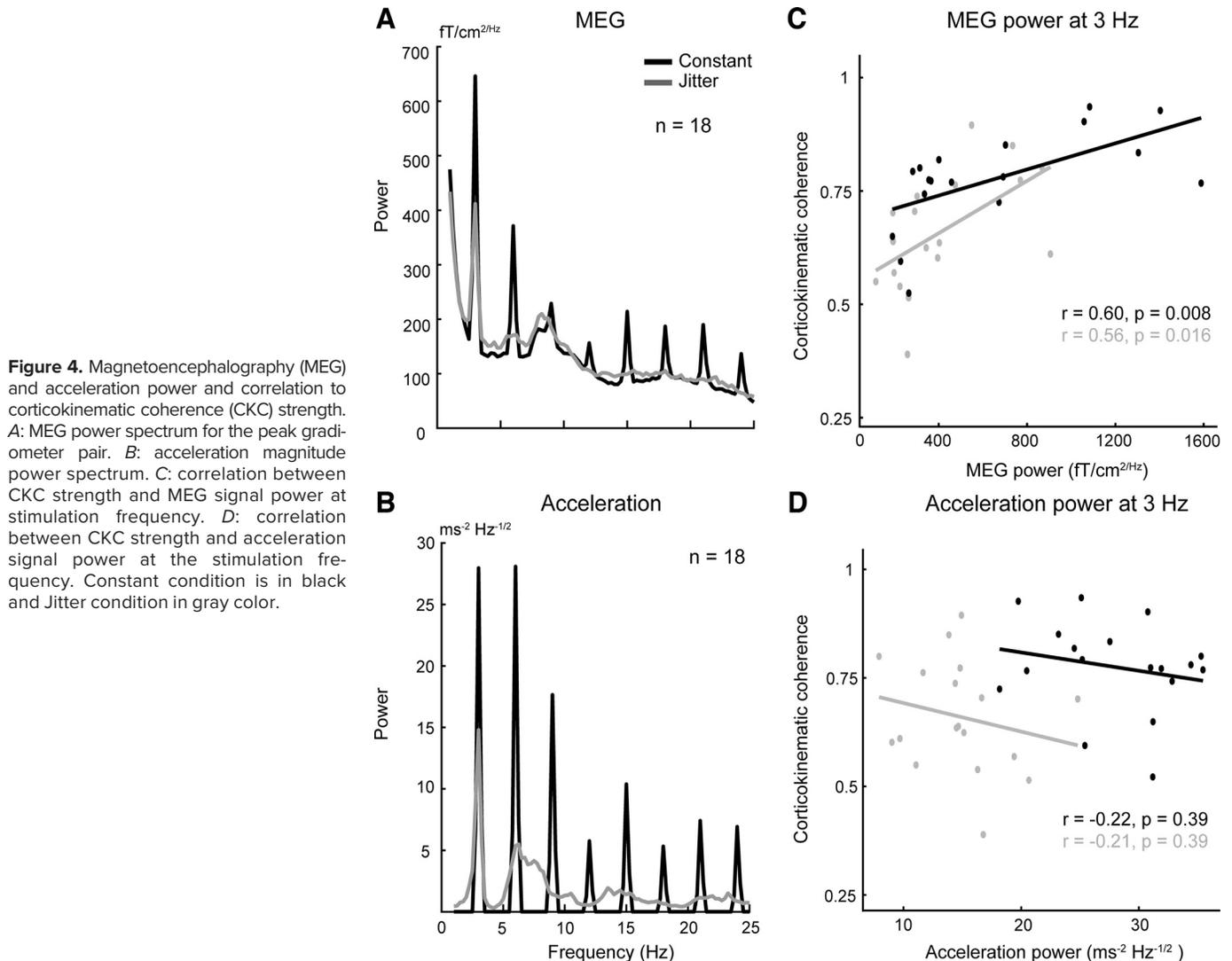
We examined how regularity of proprioceptive stimulation affects the strength of corticokinematic coherence (CKC). CKC is a method that has been used to quantify the proprioceptive afference to the SM1 cortex and the related cortical processing. In line with our hypothesis, the strength of CKC was stronger for regular than irregular proprioceptive stimulation sequence. However, both sequences resulted in strong significant CKC in accordance with previous studies using robust proprioceptive stimulators, i.e., precise movement actuators (3, 9, 10, 14) and experimenter evoked (7) or volitional movements (5–7, 11). In addition, the respective sustained-movement field amplitude to the irregular stimulation was slightly attenuated compared with the regular stimulation. The reduction in CKC strength with irregular stimulation was most likely driven primarily by the temporal variation in the stimuli, and thus wider spread of CKC in the frequency domain to several frequency bins as evidenced by the reduction in the MEG power at stimulation frequency. Thus, irregular stimulation most likely resulted in lower SNR of the stimulus-related cortical MEG signal in the 3-Hz frequency bin in which the CKC peaked.

Limited Role of Phase Coupling

CKC is the correlation between hand kinematic and MEG signals at a given frequency and peaks at the stimulation frequency (5). The cortical activity induced by proprioceptive stimulation is expected to occur with stable peripheral conduction delay irrespective of the stimulation frequency, i.e., the phase coupling between peripheral event (picked by acceleration signal) and cortical event (picked by Rolandic MEG sensors) remains constant despite the irregular stimulation sequence. Mathematically, if coherence is calculated between two non-noisy signals with events occurring randomly with a fixed delay it would lead to perfect coherence (i.e., coherence = 1) along the frequency range of the applied ISIs of the stimulus sequence. Therefore, we conclude that phase coupling most likely has only limited effect on the reduction of CKC strength during irregular stimulation observed in this experiment. The main mechanisms explaining our results appear to be the scattering of stimulus (i.e., movement) frequencies beyond the ~3-Hz peak-frequency bin and the related impairment of MEG-SNR.

Irregular Stimuli Scatter the Proprioceptive Afference to Wider Frequency Range Hindering MEG Power

Based on simulations (20), the “amplitude effect” to coherence can be expected for low SNR signals, such as MEG. The current study elaborates the previous simulation findings in



a physiological context. When irregular stimulus sequence is used, the stimulus, i.e., movement frequencies are scattered beyond the mean central movement-frequency bin. For this reason, the power of the MEG signal within the central movement-frequency bin is reduced, impairing the SNR and eventually the CKC strength. It is noteworthy that coherence is correlation in the frequency domain, and thus the temporal variation in the stimulus sequence is reflected to coherence strength partly based on the applied frequency resolution (i.e., width of each frequency bin). The weaker resolution is in theory less sensitive to temporal variation in the stimulus sequence.

In the Constant condition, the cortical response activity occurred at fixed 3-Hz frequency whereas in Jitter condition the cortical response activity ranged between 2.5 and 3.75 Hz. Given the 4,000-ms analysis window used in the coherence analysis, the frequency resolution was 0.25 Hz. Therefore, the cortical response activity/events occurred at 2.375–2.625 (~2.5), 2.65–2.875 (~2.75), 2.875–3.125 (~3), 3.125–3.375 (~3.25), 3.375–3.625 (~3.5), and 3.625–3.875 (~3.75) Hz bins of the coherence spectrum. From MEG-SNR (MEG power) and thus coherence strength perspective, a key

determinant is the number of stimulations in each frequency bin. The more stimuli, the better theoretical SNR in the MEG signal, and the stronger the CKC. In Constant condition, 100% of the stimuli (in total ~540 stimuli) occurred exactly in the ~3-Hz bin, whereas in Jitter condition only ~22% of the stimuli (~117 stimuli) occurred in the ~3-Hz bin. In case of linear relationship between number of stimuli and CKC strength, this would suggest that CKC strength in Jitter condition would be ~80% weaker from that of Constant CKC strength, but the impairment was not this pronounced in either MEG power ($31 \pm 14\%$ weaker) or CKC strength ($15 \pm 8\%$ weaker). This strongly suggest that the CKC strength is not linearly related to the number of stimuli falling into a given frequency bin. This is well-expected behavior as typically only a few or tens of stimuli are needed to obtain the main MEG response shape or amplitude when averaging strong robust somatosensory stimuli.

For the proprioceptive stimulation using pneumatic-movement actuator at 3 Hz, only 20 s of data (60 stimuli) is enough to observe the response shape and reach the nearly maximal SNR (3). Afterward, this ceiling of the SNR evolves slowly, and thus additional stimuli only weakly enhance the

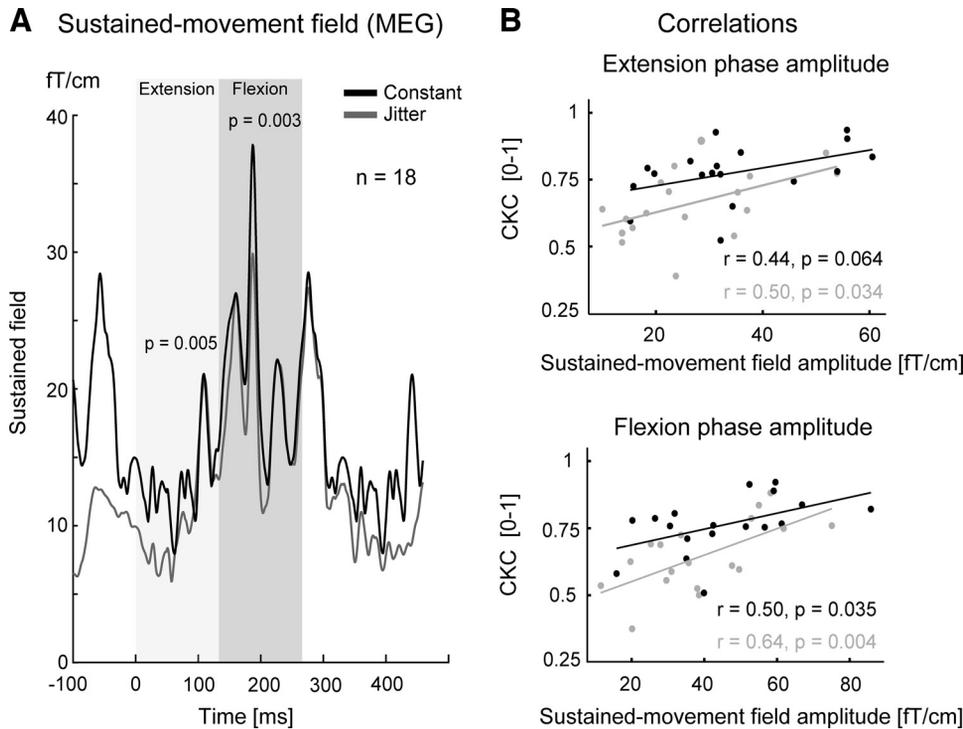


Figure 5. Grand average sustained-movement fields and correlations between corticokinematic coherence (CKC) and the evoked fields. *A*: sustained-movement fields for Jitter (gray) and Constant (black) conditions. The highlighted areas combined were used to compute acceleration magnitude for the movement cycle. *B*: correlation between CKC strength and the sustained-movement field of finger extension (*top*) and for finger flexion (*bottom*) movement. MEG, magnetoencephalography.

SNR. The number of stimuli needed to observe significant CKC is expected to be relatively small, as CKC strength has shown to be maximized already after 1-min (180 stimuli) of 3-Hz index finger stimulation (3). During irregular Jitter condition, only ~117 stimuli fell into the ~3-Hz bin (~540 in Constant condition), which most likely primarily explains the weaker coherence. It is noteworthy that the stimuli falling into two adjacent bins from the ~3-Hz bin (~2.75 Hz: ~130 stimuli and ~3.25 Hz: ~100 stimuli) could have partly contributed to peak CKC strength, due to some possible temporal instability in the neuronal coupling between periphery and cortical activity.

Regularity of Stimulation Sequence May Enhance Amplitude Coupling

In contrary to our hypothesis, the sustained-movement fields were stronger in Constant than Jitter condition. This is opposite behavior when compared with intermittent sensory stimulation at long ISIs (seconds). It is well demonstrated that longer ISI enhances the amplitude of an evoked MEG field in all sensory modalities, e.g., for auditory stimuli from 1 s to 16 s (33), visual stimuli from 150 ms to 40 s (34), electrical stimulation of the median nerve (i.e., to somatosensory stimulus) from 150 ms to 5 s (24), and proprioceptive stimuli from 500 ms to 16 s (4). Sensory stimulus is known to induce a neuronal “trace” in the brain, and the recovery from the prior stimulus can be modeled by stimulus “lifetime” (35). The lifetime for proprioceptive stimulation is ~2 s (4). Amplitude of a sensory-evoked field to electrical stimulation of the median nerve (i.e., to somatosensory stimulus) have shown to be at similar low level with very short ISIs of 150 and 300 ms, and the amplitude is increased only with longer intervals of 1, 3, and 5 s (24). Therefore, the previous stimulus or stimuli are still reducing the response to a subsequent

stimulus during repetitive stimulation with short ISI (25). In the current study with a continuous movement stimulus, a very short ISI (333 ms) was applied, and likely because of this the introduced ±20% (±66 ms) jitter had only a small effect on the sustained-movement field amplitude. Given the 2-s lifetime for proprioceptive stimulation, the introduced jitter was not temporally effective enough to counter the effect of the previous stimuli, and thus enhance the sustained-movement field, and ultimately the CKC strength. For effective function, ISI of ~2 s or more would have been needed (4), which is not feasible for CKC method.

Random jitter is typically introduced in evoked designs to prevent anticipation of the stimulus that is hypothesized to diminish the response amplitude (22, 23). Instead, in this experiment the sustained-movement field was slightly stronger in Constant condition suggesting an importance of temporal stability of the stimulation for CKC method and its implementation in functional mapping, etc. Indeed, when sensory stimuli, auditory or visual, are presented in a rhythmic fashion it can improve sensory perception (36). The temporal expectation of sensory stimuli enhances neural excitability to the anticipated sensory event (37, 38). In the somatosensory domain, using actual and omitted stimulations Andersen and Lundqvist (39) showed that when a participant is expecting a tactile stimulus to occur, but it is omitted, a time-locked response appearing in the secondary somatosensory cortex and insula highlights the capability of the brain to maintain temporal sensory representations based on previous sensory events.

Topographical representation reveals that peak activity occurred in the contralateral SM1 as expected (3, 5, 7, 9, 11). Furthermore, the spatial distribution was nearly identical between the conditions suggesting that both conditions activated the same or very similar group of SM1 cortex neurons.

Finally, we suggest that the temporally fixed constant proprioceptive stimulation can further enhance the CKC strength due to better amplitude coupling of coherence by inducing stronger respective sustained-movement field amplitudes and greater MEG power.

Effects of Irregularity Were Emphasized at the First Harmonic Frequency

Typically, strong CKC is observed at harmonics of its fundamental (stimulation) frequency, especially when precise proprioceptive stimulators (movement actuators) are used (3, 10). In this experiment, the first harmonic was at 6 Hz, in which the CKC strength was on average 22% (SD: $\pm 26\%$) and 57% ($\pm 21\%$) lower than at 3 Hz in Constant and Jitter conditions, respectively. Irregular stimulation emphasized the reduction of CKC at the first harmonic and indicates the importance of stable stimuli when optimizing for CKC strength estimation. During the Jitter condition, the proprioceptive stimulation varied between ~ 2.5 and 3.75 Hz (1.25 Hz band) with an average at 3 Hz. However, at 6 Hz (the first harmonic), the effect of jitter was twofold in the frequency domain, spanning the harmonic frequencies between ~ 5 and 7.5 Hz (2.5 Hz band). Consequently, the CKC strength was diminished at ~ 6 Hz bin and was demonstrated with a visually wider but flattened coherence peak. In this case, only 12% (65 stimuli) of the stimuli fell into the ~ 6 -Hz bin. At the second harmonic (9 Hz), the CKC did not even reach the significance level in the Jitter condition but was well detectable in the Constant condition.

Finally, coherence analysis in CKC has typically been performed using 2-s epochs (4-s in the current experiment) resulting in frequency resolution of 0.5 Hz (5–7, 9, 11). We chose to use more accurate 0.25-Hz frequency resolution to better detect the effects of irregular stimulation. We repeated our CKC analysis using 2-s epochs, and the results were identical. Thus, our observations and conclusions are not dependent on the chosen analysis window length.

Perspectives

The current work extends the knowledge on how to optimally use CKC method to 1) quantify proprioceptive afference, 2) efficiently map the hand functional representation area, and 3) probe proprioceptive pathways in humans (40). It is noteworthy that also irregular stimulus sequence (Jitter condition) resulted in robust significant CKC in all our participants at stimulation frequency. Although only $\sim 22\%$ of the stimuli fell into the 3-Hz frequency bin during the Jitter condition, the reduction in MEG power and CKC strength was much less than expected ($\sim 80\%$ expected vs. $\sim 15\%$ observed reduction in CKC). Therefore, the irregular stimulation sequences are also feasible to quantify CKC, especially if the number of stimuli at the frequency bin of interest remains sufficiently constant. Furthermore, the coherence spectrum yielded from the Jitter condition resembled the ones obtained in CKC studies using volitional or manually evoked (by experimenter) movements (5–7, 11, 12, 16, 21). The coherent band is visually wider with less distinctive peak, especially at the harmonic frequencies compared with studies using precise constant stimulation sequence evoked by the movement actuators (3, 10). We recommend that for

robust and reproducible quantification of CKC, precise proprioceptive stimulators (movement actuators) are used (9, 14). However, the active or experimenter-executed movements may also be utilized if enough (>100) or approximately similar number of repetitions/stimuli between the experimental conditions/sessions are collected. In addition, CKC strength is not significantly affected by choice of stimulation frequency using voluntary (21) or actuator-evoked movements (3), and CKC can be quantified using basically any signal picking the rhythmicity of the movement or action, e.g., electromyography or force signal (6), allowing freedom in designing the research setting or clinical examination.

CKC has excellent reproducibility using both MEG (9) and EEG (14) when the proprioceptive stimulators are used. Therefore, CKC measurements are applicable in longitudinal designs or in clinical settings where the interest is, e.g., to follow a progression of disease or effects of rehabilitation. The stimulators are especially suitable for several patient groups who have motor impairments and thus difficulties in performing active stable volitional movements (stroke, paralysis, spinal cord injury, infants, etc.). As was evidenced in this study, even a slight temporal variation in movement leads to a significant reduction in CKC strength. In addition, interindividual variation appeared to increase in Jitter condition which can hinder the detection differences both in individual and group levels. Therefore, when quantifying the cortical proprioceptive processing using CKC method in different diseases (16) or between populations (10), a constant movement sequence using pneumatic movement actuators is recommended.

Conclusions

Our results highlight the importance of temporal stability in the proprioceptive stimulation sequence when quantifying the level of cortical proprioceptive processing using CKC strength. Phase coupling (i.e., the delay of proprioceptive afference from the periphery to the brain) has a negligible effect on CKC strength because it is hypothesized to remain constant during regular and irregular stimulation sequences. Furthermore, the irregular stimulation causes the proprioceptive afference and the related cortical activity to scatter in frequency domain to several frequency bins that in turn reduces the SNR in the mean (i.e., peak) stimulation frequency bin, and thus hinders the peak CKC strength through weaker amplitude coupling of coherence. However, also irregular stimulation sequence leads to robust and significant coherence, and therefore can be used to map the cortical representation of the hand area and quantify the CKC strength as far as sufficient and similar number of stimuli/actions are performed.

DATA AVAILABILITY

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

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

T.N. and H.P. conceived and designed research; T.N. and H.P. performed experiments; T.M., T.N., and H.P. analyzed data; T.M. and H.P. interpreted results of experiments; T.M. and H.P. prepared figures; T.M. and H.P. drafted manuscript; T.M., T.N., and H.P. edited and revised manuscript; T.M., T.N., and H.P. approved final version of manuscript.

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