Feasibility and reproducibility of electroencephalography-based corticokinematic coherence

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Abstract

Corticokinematic coherence (CKC) is the phase coupling between limb kinematics and cortical neurophysiological signals reflecting cortical processing of proprioceptive afference, and is reproducible when estimated with magnetoencephalography (MEG). However, feasibility and reproducibility of CKC based on electroencephalography (EEG) is still unclear and is the

primary object of the present report. Thirteen healthy right-handed volunteers (7 females, 21.7 ± 4.3 years) participated two separate EEG sessions 12.6±1.3 months apart. Participants' dominant and non-dominant index finger was continuously moved at 3 Hz for 4 min separately using a pneumatic-movement actuator. Coherence was computed between finger acceleration and three derivations of EEG signals: (1) average reference, (2) bipolar derivations, and (3) surface Laplacian. CKC strength was defined as the peak coherence value at the movement frequency. Intraclass-correlation coefficient values (0.74–0.93) indicated excellent inter-session reproducibility for CKC strength for all derivations and moved fingers. CKC strength obtained with EEG was ~2 times lower compared to MEG but the values were positively correlated across the participants. CKC strength was significantly ($p<0.01$) higher for bipolar (session-1 0.19±0.09; session-2 0.20±0.10) and surface Laplacian (session-1 0.22±0.09; session-2 0.21±0.09) derivations than for the average reference (session 1 0.10±0.04; session 2, 0.11±0.05). We demonstrated that CKC is feasible and reproducible tool to monitor proprioception using EEG recordings, although the strength of CKC was twice lower for EEG compared to MEG. Laplacian and bipolar (CP3-C1/CP3-C3 and CP4-C2/C4-FC2) EEG derivation(s) are recommended for future research and clinical use of CKC method.

Keywords: proprioception; kinematics; electroencephalography; somatosensory; repeatability

New & Noteworthy

The most important message of this report is that the corticokinematic coherence (CKC) method is feasible and reproducible tool to quantify, map and follow cortical proprioceptive ("the movement sense") processing using EEG that is more widely available for CKC recordings than previously used MEG designs, especially in clinical environments, but also for basic research. We provide useful recommendations for optimal EEG derivations for cost-effective experimental designs allowing large sample size studies.

Introduction

Corticokinematic coherence (CKC) quantifies the coupling between oscillatory cortical activity measured with electrophysiological recordings and limb kinematics (*e.g.* acceleration) that occurs during repetitive rhythmic voluntary (Bourguignon et al., 2012b, 2011; Jerbi et al., 2007), passive (Piitulainen et al., 2013b, 2015, 2018a), and observed (Marty et al., 2015; Bourguignon et al., 2012a) movements. CKC peaks at movement frequency and its harmonics, and it can be measured using various peripheral movement-related signals and motor tasks (Piitulainen et al., 2013a), and movement rates (Marty et al., 2015; Piitulainen et al., 2015). CKC primarily reflects proprioceptive processing in the primary sensorimotor (SM1) cortex (Bourguignon et al., 2015; Piitulainen et al., 2013b) with an apparent latency of 50–100 ms that corresponds to the timing of the strongest deflection of the cortical movement-evoked field (Piitulainen et al., 2015). CKC has been mainly studied in response upper limb movements but it can also be measured using ankle (Piitulainen et al., 2018a) or toe movements (Piitulainen et al., 2015).

CKC is a promising tool for clinical evaluation of the integrity of cortical proprioceptive processing. Passive movements have been previously used to probe the recovery of sensorimotor functions after stroke (Parkkonen et al., 2017), but CKC could provide the clinicians with essential information about changes in the cortical proprioceptive processing to better target stroke rehabilitation to restore upper and lower limb functions. Another potential clinical use is non-invasive pre-surgical functional mapping of SM1 cortex (Bourguignon et al., 2013). CKC can be used to identify the SM1 cortex even in the presence of strong magnetic artifacts arising from cranial clips or tooth braces in magnetoencephalographic (MEG) recordings (Bourguignon et al., 2016). Other potential applications of CKC lay in the investigation of the development of proprioception across the lifespan (Piitulainen et al., 2018a), and its alteration in various sensorimotor impairments, e.g., cerebral palsy, neuropathy, spinal cord injury, Friedreich ataxia, etc. (Naeije et al., 2020; Lamartine Monteiro et al., 2020; Marty et al., 2019).

In initial CKC studies, CKC was estimated in response to voluntary or experimenter-evoked passive movements (Bourguignon et al., 2011; Piitulainen et al., 2013a; Piitulainen et al., 2013b). But movements made by humans vary in amplitude, frequency and regularity between sessions, days, and experimenters. These sources of variability are a severe limitation for studies aimed at comparing populations with different motor skills and for longitudinal studies. To overcome this limitation, an accurate computer-controlled and MEG-compatible movement actuator was developed for reproducible movements across time (Piitulainen et al., 2015). Using this actuator, we have shown that CKC can be reproducibly estimated from MEG recordings, with high consistency across sessions performed one year apart, especially at the group level (Piitulainen et al., 2018b). CKC to accurately timed movements is thus a suitable tool for longitudinal studies.

Although MEG is likely to be the technique of choice to estimate CKC, its availability is still limited, and it comes at a high cost. Electroencephalography (EEG) is an obvious potential alternative to MEG as it is more widely available, cheaper, and more versatile. Although it has been demonstrated in newborns that CKC can be estimated based on EEG recordings (Smeds et al., 2017b), there are no studies yet to determine the reliability and reproducibly of such estimation. Recommendations for EEG electrode configurations to guide the large-scale utilization of CKC are also missing.

Our aim was to examine the reliability and reproducibility of CKC estimated from EEG signals using passive index finger movements evoked by a computer-controlled pneumatic movement actuator in a one-year follow-up study on healthy young adults. A long enough follow-up period was chosen, since detectable changes in cortical proprioceptive processing induced by most pathologies or rehabilitation techniques are expected to occur in time-ranges of months or years. We also aimed to examine if CKC strength and its reproducibility differ between the dominant

99 and non-dominant hand. Finally, we aimed to provide recommendations for recording and
100 computing CKC when using EEG.

101 Methods

102 Participants

103 We studied 13 healthy right-handed volunteers (mean ± SD age, 21.7 ± 4.3 years; 7 females)
104 who did not report any history of movement disorders or neuropsychiatric disease. Their
105 Edinburgh handedness inventory score (Oldfield, 1971) was 87.2 ± 11.4 on the scale from –100
106 to 100. The study had prior approval by the ethics committee of Aalto University. The
107 participants gave informed consent before participation. One participant was excluded due to the
108 presence of intractable artifacts in the EEG recordings. Thus, the results are reported for the
109 remaining 12 participants.

110 We have previously reported the reproducibility of CKC based on the MEG data recorded from
111 the same volunteers (Piitulainen et al., 2018b). The present study focuses on the analysis of the
112 EEG signals that were simultaneously recorded with MEG.

113 Experimental protocol

114 A custom-made non-magnetic pneumatic movement actuator (Aalto NeuroImaging, Aalto
115 University, Espoo, Finland) was used to generate passive dominant and non-dominant index
116 finger flexion-extension movements of the metacarpophalangeal joint. The movement actuator
117 has been fully described in (Piitulainen et al., 2015) and similar designs have been successfully
118 used in MEG (Piitulainen et al., 2018b; Smeds et al., 2017a; Bourguignon et al., 2016; Vinding
119 et al., 2019; Illman et al., 2020), EEG (Smeds et al., 2017b) and fMRI (Nurmi et al., 2018; Lolli
120 et al., 2019) studies. Index finger was attached to a pneumatic artificial muscle (DMSP-10-100
121 AM-CM, Festo AG & Co, Esslingen, Germany) that moved downward in vertical direction when

its internal air pressure was increased to 4 bar thus flexing the finger, and then extending it back to the initial position when the air pressure was released. In this way, continuous passive flexion–extension movements were generated at 3 Hz for the dominant and non-dominant index finger separately (4 min for each finger in separate sessions). The movement range was ~5 mm. Movement frequency was set to 3 Hz because it has been found appropriate and efficient for robust CKC estimation (Piitulainen et al., 2015).

During the MEG/EEG recordings, participants were sitting with the stimulated hand on the upper plate of the movement actuator that was placed on the table in front of them (Fig. 1). The index finger was taped to the aluminum end of the pneumatic muscle. The other hand was resting on the thigh. Earplugs were used to block the slight concomitant auditory noise that arose from the airflow within the pneumatic muscle. A white A3-sized cardboard sheet was taped horizontally to the MEG gantry to prevent the participant from seeing the moving finger. Participants were instructed to fixate, through a rectangular hole in the cardboard sheet, a picture on the wall of the magnetically shielded room, 2.2 m in front of the eyes. In order to estimate reproducibility of CKC, the recordings were performed in two sessions 12.6 ± 1.3 months apart.

Measurements

EEG/MEG. The measurements were carried out at the MEG Core, Aalto NeuroImaging, Aalto University (Espoo, Finland) inside a magnetically shielded room (Imedco AG, Hägendorf, Switzerland). EEG signals were recorded simultaneously time-locked with MEG and acceleration signals. The MEG device was a 306-channel whole-scalp neuromagnetometer (Elekta Neuromag™, Elekta Oy, Helsinki, Finland). Reproducibility results for MEG data have been previously reported in (Piitulainen et al., 2018b). EEG was recorded with a MEG-compatible cap (ANT Neuro waveguard™ original), containing 58 Ag-AgCl surface electrodes mounted according to the international 10–20 system with modified combinatorial nomenclature. EEG electrodes were referenced with respect to AFz-electrode. EEG signals were band-pass

filtered at 0.1–330 Hz and sampled at 1 kHz. The output impedance of the EEG electrodes was kept below 10 kΩ.

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

Data Processing

Preprocessing. EEG data was first visually inspected to identify noisy channels. Then, principal component analysis using MNE-Python toolbox was used to remove two EEG components related to eye blink artefacts (Gramfort et al., 2013). Noisy EEG channels were replaced with the average of all neighboring EEG channels using FieldTrip toolbox function ft_channelrepair (Oostenveld et al., 2011). Then the 58 raw EEG signals (referenced to AFz electrode) were spatially filtered using (1) the *average reference* of all EEG channels (excluding the EEG channel of interest), (2) all possible single differential (*bipolar*) combinations between the 58 EEG signals (in total 1653 combinations), and (3) surface *Laplacian* derivation. The coherence analysis was performed separately for all the resulting EEG signals (see details below).

Coherence analysis. For coherence analyses, the continuous data were split into 2-s epochs with 1.6-s epoch overlap, leading to a frequency resolution of 0.5 Hz (Bortel and Sovka, 2007). EEG epochs with signals exceeding 200 mV were excluded to avoid contamination of the data by internal or external noise sources. We then performed coherence analysis (Halliday et al., 1995)—yielding cross-, power- and coherence spectra—between EEG signals and the Euclidian norm of the three orthogonal accelerometer signals. Before the coherence analysis, each epoch of acceleration was normalized by its Euclidian norm (Bourguignon et al., 2011). The magnitude squared coherence was chosen as coupling measure as done in our previous CKC studies (Bourguignon et al. 2011, 2015, 2016; Marty et al. 2019; Piitulainen et al. 2013a, 2013b, 2015,

2018a, 2018b). Other coupling measures dealing with potential brain-peripheral delays (such as, *e.g.*, phase locking value) are expected to yield similar results.

CKC strength was defined as the maximum coherence value at 3 Hz across the 32 EEG electrodes contralateral to the movement for average reference and surface Laplacian approaches or across all the 1653 bipolar EEG signals. The maximum channel (or channel pair) was defined independently for session 1 and session 2 data. Group-level topographic distributions of CKC were visualized for the Laplacian and average reference approaches using FieldTrip toolbox (Oostenveld et al., 2011).

Finger kinematics. Acceleration signals were extracted and averaged with respect to the movement onsets, separately for each individual, finger, and session. The resulting acceleration signals were filtered through 1–195 Hz. Then, magnitude and regularity of the evoked movements were estimated by computing the mean and coefficient of variation of peak acceleration magnitude (*i.e.* Euclidian norm of the three orthogonal acceleration signals) across all evoked movements.

Statistical analyses

Statistical significance of coherence. The statistical significance of individual coherence levels (maximum value across the 32 or 1652 EEG signals of interest) was assessed under the hypothesis of linear independence of Fourier coefficients from epoch to epoch at each frequency of interest, taking into account the use of overlapping epochs (Halliday et al., 1995; Bourguignon et al., 2011). To correct for multiple comparisons, the alpha level was set to 0.05/Ns, Ns = 32 (midline and contralateral channels to stimulus) or 1652 (all possible bipolar combinations) being the number of EEG signals included in the analysis. Note that in the case of bipolar derivations, this is an extremely conservative limit as there are naturally much less degrees of freedom than pairs of electrodes.

196 *Reproducibility and analysis of variance.* These statistical analyses were performed in IBM
197 SPSS Statistics software (ver. 25). To enable comparison with other studies, we used common
198 and closely related tests to assess inter-session reproducibility for CKC strength. A two-way
199 mixed-effects model intraclass-correlation coefficient (ICC) and Spearman correlation
200 coefficient were computed between the session 1 and session 2 CKC values. Reproducibility for
201 the evoked passive movements (finger kinematics) has been reported earlier (Piitulainen et al.,
202 2018b).

203 We assessed the effect of EEG-derivation, moved hand and session on CKC strength. Due to
204 small sample size (n = 12), we used non-parametric related samples test to this effect: a
205 Friedman test was used to compare CKC strength between the three different EEG derivations,
206 and a Wilcoxon two-related-samples test was used to compare CKC strength between specific
207 EEG-derivation, hands or sessions.

208 ## Results

209 *Data quality.* The movement actuator and accelerometer did not produce notable artifacts in the
210 EEG signals. The noisy EEG channels (mean ± SD 6 ± 3, range 3–13) were replaced with the
211 average of neighboring channels. All recordings were successful with 573 ± 45 (session 1; mean
212 ± SD) and 572 ± 29 (session 2) artefact-free epochs collected for dominant hand stimulation, and
213 525 ± 58 (session 1) and 566 ± 35 (session 2) for the non-dominant hand. These numbers of
214 epochs did not differ significantly between the hands or sessions ($ps > 0.05$; Wilcoxon tests).

215 The kinematics of the evoked movements were stable. Indeed, in (Piitulainen et al., 2018b) we
216 report a peak acceleration magnitude of 0.93 ± 0.04 m/s^2 (session 1; mean ± SD) and 0.92 ± 0.04
217 m/s^2 (session 2) for dominant hand, and 0.91 ± 0.04 m/s^2 (session 1) and 0.92 ± 0.04 m/s^2
218 (session 2) for non-dominant hand.

Strength of CKC at the group level. Figure 2 shows the spectra of CKC averaged across subjects for all fingers, spatial filters, and recording sessions. Qualitatively, CKC strength at 3 Hz was strikingly similar between the two measurements separated by 12.6 ± 1.3 months. CKC at harmonic frequencies also appeared very reproducible at the group level. At the individual level, 8–12 out of 12 participants showed significant CKC at 3 Hz depending on the EEG-derivation used, hand examined and session (see Table 1). In addition, we did compute CKC for the data referenced to AFz, but it resulted very weak values that were significant in only 3 out of 12 participants ($p < 0.05$). Thus, we did not consider the monopolar EEG results further.

Table 1 present the CKC strength for all hands, tested derivations, and recording sessions. Figure 3 presents CKC strength when the right and left hands were pooled together. CKC remained at similar level between the *sessions* (Laplacian, $p = 0.81$ and $p = 0.53$; average reference, $p = 0.084$ and $p = 0.70$; bipolar, $p = 0.53$ and $p = 0.31$ for dominant and nondominant hands respectively) and *hands* (Laplacian, $p = 0.81$; average reference, $p = 0.88$; bipolar, $p = 0.75$) but differed between the *EEG-derivations* ($ps < 0.002$). CKC strength was higher for Laplacian and bipolar EEG-derivations compared to the average reference approach for both sessions and tested hands ($ps < 0.005$).

Reproducibility of CKC. Figure 4 illustrates the reproducibility of individual values of CKC strength. In general, participants with strong CKC at session 1 showed strong CKC also at session 2 and *vice versa*. Nevertheless, CKC strength changed by over 0.1 between sessions in 1–2 out of 12 participants depending on the EEG derivation and hand. CKC strength based on EEG recordings correlated positively with the CKC strength obtained from simultaneous MEG recordings (Fig. 4b).

Table 2 presents the reproducibility values for CKC for the three different derivations tested. ICC values between session 1 and session 2 indicated excellent (≥ 0.74) inter-session reproducibility for CKC strength both for the dominant and non-dominant hand. However,

Spearman correlation tests between session 1 and session 2 were significant only for the non-dominant hand when average reference or bipolar approaches were used.

Topographic distribution of CKC at the group level. Figure 5 shows the topographic distributions of the grand-average CKC values for the dominant and non-dominant hands in session 1 and session 2. As expected for neural sources in the primary sensorimotor cortex, CKC peaked at EEG electrodes close to C3/C4 contralateral to the moved finger.

Optimal bipolar EEG derivation. Figure 6 presents the EEG-electrode pairs showing the strongest CKC. Among all the possible 1653 bipolar EEG pairs, two appeared to be optimal for CKC estimation. For the dominant hand (right hand stimulation) CKC peaked at the pairs CP3–C1 and CP3–C3 in 58% of the cases (8 and 6 respectively out of 24 cases). For the non-dominant hand, CKC peaked at the pairs C2–CP4 and FC2–C4 in 70% of the cases (10 and 7 respectively out of 24 cases).

Discussion

We examined the reproducibility of CKC derived from EEG recordings for movements elicited by a pneumatic movement actuator. We observed significant CKC in all studied participants, but this depended on the EEG derivation applied, and CKC was generally weaker compared to previous studies using the same stimulus in MEG (Piitulainen et al., 2018b; Piitulainen et al., 2015). The reproducibility of CKC strength was good or excellent at the group level. However, there were several participants who showed some inter-session variation, and thus caution needs to be taken if the aim is to follow CKC in single individuals using EEG. Our results indicated that EEG is a feasible tool to examine and follow cortical proprioceptive processing in longitudinal studies. Finally, a one bipolar EEG-channel approach following our EEG-pair suggestions shows potential as a cost-efficient tool to follow cortical proprioceptive processing in larger populations, *e.g.*, in clinical studies.

Reproducibility of CKC when using EEG

The reproducibility of CKC strength (tagging cortical proprioceptive processing) at the group level was good to excellent between two sessions 1-year apart. This is an encouraging result, as the test-retest reproducibility of evoked potentials to cutaneous electrical stimulation of the tactile receptors of the fingers has been reported to be low, even in 'ideal' condition without detaching the EEG cap between consecutive recordings (Kalogianni et al., 2018). However, the source localizations of evoked potentials to tactile (Schaefer et al., 2002) or median nerve (Kristeva-Feige et al., 1997) stimulations have proven highly reproducible. The topographic distributions for the current proprioceptive stimuli appeared very similar across sessions, suggesting that our protocol could be well suited to compare groups for longitudinal effects. Large longitudinal effects on CKC strength could be expected. Healthy ageing appears to enhance CKC strength by almost 80%, based on cross-sectional comparison of older (~69 years) with young adults (~25 years) (Piitulainen et al. 2018a). Presumably, even larger effects are possible in clinical populations. The change in CKC strength for the current 1-year follow-up was ~5%, thus all intervention effects exceeding this level would presume to be detected.

There was no marked difference between the hands in terms of CKC reproducibility. The correlation coefficients between sessions of CKC strength appeared slightly higher for the non-dominant hand, but a non-parametric permutation test (in which values for the dominant and non-dominant hands were randomly permuted within subjects to derive a permutation distribution) indicated that the difference between hemispheres in the inter-session correlation was not statistically significant ($ps > 0.2$). The reproducibility was very similar for different EEG derivations, although the CKC strength was clearly weaker for the average reference. Thus, it appears that from the reproducibility point of view the choice of EEG derivation is not crucial, but it is natural to recommend using the derivations that maximize the CKC strength (Laplacian or bipolar).

The major factor affecting the reproducibility of CKC is most likely the careful preparation of the EEG electrodes maximizing the EEG signal-to-noise ratio. The EEG electrode locations at the scalp should be fixed as well as possible between the sessions, and their impedance should be confirmed to be low enough. We did not use any advanced methods for the placing the EEG cap in our participants but paid particular attention to preparation of the electrode-skin contacts, likely reducing random variability in the data being crucial for all longitudinal studies. The proprioceptive stimuli evoked by the pneumatic movement actuator are shown to be very reproducible from stimulus-to-stimulus, participant-to-participant, and session-to-session (Piitulainen et al., 2018b). Only finger and hand positioning on the stimulator is a potential source of variability in CKC strength attributable to the simulation procedure. Hence, provided care is taken, the CKC strength should be minimally related to variations in stimulation parameters.

Our results indicate that CKC strength may vary from session-to-session at the level of the individual participant, but the individuals with strong CKC in the first session tended to have strong CKC also in the second session, and v*ice versa*. Indeed, the CKC strength correlated positively between the sessions, being significant for 2 in instances out of the 6 (2 hands × 3 derivations). Thus, EEG-based CKC approach is reproducible tool to follow the cortical proprioceptive processing in longitudinal studies, but individual patient results should still be interpreted with some caution. It could be recommended that future studies could measure the same participant multiple times in sessions separated by few hours/days; the rational being that CKC strength should prove more reproducible when assessed based on multiple than single sessions.

Inter-individual variability in CKC strength

In line with previous studies, CKC showed high inter-individual variation (Piitulainen et al., 2015, 2013b, 2018b; Bourguignon et al., 2011). The mechanisms for the variation are unclear but

318 do not seem to be attributable solely to MEG or EEG methodological constraints, as the variation
319 is evident in both methods with different constraints. For example, MEG is more prone to
320 alterations in the head orientation and distance with respect to MEG sensors between the session.
321 CKC strength clearly reflects changes in the brain functions, as older individuals show stronger
322 CKC than younger ones in association to worse postural balance performance (Piitulainen et al.,
323 2018a). However, the sources of the high inter-individual variation in the CKC strength (*i.e.*
324 cortical proprioceptive processing) still need to be clarified.

325 **Impact of EEG derivation scheme on CKC strength**

326 CKC was stronger when estimated from Laplacian and bipolar derivations compared to average
327 reference. These clear differences in CKC strength indicate a difference in the signal-to-noise
328 ratio (SNR) of the EEG signals for these derivations. Indeed, based on simulations, an increase
329 in low SNR signal amplitude increases the level of coherence (Muthukumaraswamy and Singh,
330 2011). Such SNR–coherence relationship is also easily shown from theoretical considerations.
331 The advantage of Laplacian EEG and bipolar derivations are their enhanced spatial selectivity
332 when compared to average reference derivation. Higher spatial selectivity may enhance the SNR
333 arising from the SM1 cortex contralateral to the stimulus. The further advantage of using
334 multiple bipolar electrode-pairs is the exploration of all possible bipolar derivations (in our case
335 1653 pairs of EEG electrodes) that increases the probability of identifying the optimal derivation
336 for a given stimulus and individual. But this approach comes with increased computational
337 burden and increased risks of false positives. In contrast, the Laplacian approach is
338 computationally more straightforward and requires less stringent control for multiple
339 comparisons. The average reference derivation affords a lower spatial selectivity and hence is
340 fraught with poorer SNR and CKC strength. Even worse results were obtained with monopolar
341 EEG, *i.e.*, when referenced to AFz (< 25% of the participants reached the statistically significant
342 CKC).

CP3-C1 or CP3-Fz electrode pairs are the recommended derivations to look at somatosensory evoked potentials to right hand stimuli (Cruccu et al., 2008). In line with this recommendation, we identified CP3-C1 as the most common optimal derivation in our population. The CKC did not peak in CP3-Fz electrode pair in our participants, and this electrode pair reached significant CKC level only in 15% of the participants. Therefore, the recommendations by Cruccu at al. (2008) are valid also for CKC recordings but if single channel EEG recordings are used, we recommend the derivation CP3–C1 or CP3–C3 as the electrode placements. However, if abnormal cortical anatomy is expected, e.g. due to cortical lesions, single channel EEG approach may fail to detect significant CKC, and thus it would be recommended to use a larger set of EEG electrodes (minimum 32) and a Laplacian derivation approach to pinpoint the peak CKC channels. Note also that a common feature of most of the optimal derivations is to involve electrode pairs for which one is posterior and lateral to the other.

There is one prior CKC study using EEG, although to manually evoked movements in infants at the neonatal intensive-care environment (Smeds et al., 2017b). In the infants, CKC peaked only at first harmonic of movement frequency (Smeds et al., 2017b), whereas adults typically show strong CKC both at the movement frequency and its first harmonic both to experimenter (Piitulainen et al., 2013b) and actuator evoked (Piitulainen et al., 2015, 2018b; Bourguignon et al., 2016) finger movements. This discrepancy may arise from uncompleted neurodevelopment and therefore less discrete movement directional specificity (extension *versus* flexion) in infants.

CKC strength in EEG vs. MEG

CKC strength obtained in the same session and recording with EEG and MEG were highly correlated, although the CKC strength obtained with EEG (most optimal Laplacian derivation) was about two times lower than the one obtained with MEG recordings. This difference in CKC strength between the modalities probably pertains to differences in spatial selectivity of the techniques (Hämäläinen et al., 1993), leading to differences in SNR and estimated coherence

strength. Nevertheless, our results indicate that EEG can be used to quantify CKC as surrogate to MEG recordings, which expands clinical utilization of CKC method by providing a more cost-efficient and accessible recordings.

Since significance thresholds for coherence estimates decrease asymptotically as the inverse of the number of data epochs (Halliday et al., 1995), it can be inferred that EEG recordings need to be 2 times longer than MEG recordings to uncover significant CKC (Destoky et al., 2019). Similar findings were previously reported for the coupling between brain activity and the temporal envelope of heard speech (Destoky et al., 2019). As fully developed in this latter reference, significant effects in a broad range of cortical functions are typically detectable with EEG if there is 2–4 times longer recording than in MEG.

Perspectives

CKC can extract the somatosensory component of the corticospinal coupling during passive movement stimuli, particularly the proprioceptive processing in the SM1 cortex (Bourguignon et al., 2015; Piitulainen et al., 2013b). Therefore, CKC is applicable also in paralyzed patients and to examine and follow changes in cortical proprioceptive processing, *e.g.*, during stroke recovery, motor-skill acquisition, sensorimotor development, and aging. High reproducibility is a prerequisite for longitudinal studies. The reproducibility of EEG-based CKC at group level was good or excellent, and thus enables its use in the longitudinal studies, but individual patient results should be interpreted with some caution. Another advantage of CKC is that the cortical signals are relative robust, and thus CKC can be detected in most if not all individuals. Finally, the applicability of EEG to measure CKC will expand the research and clinical use of the CKC method.

Conclusions

Our results demonstrate that CKC elicited with a pneumatic movement actuator can be reliably and reproducibly estimated from EEG recordings. Thus, EEG-based CKC approach shows potential as a tool to follow the cortical proprioceptive processing in longitudinal studies. However, some caution needs to be taken if the aim is to follow single individuals. Laplacian and bipolar EEG derivation(s) are recommended for future research and clinical use of the CKC method. A cost effective CKC recording using only few bipolar EEG channels was also suggested. For this purpose, we recommend the use of CP3-C1/CP3-C3 and CP4-C2/C4-FC2 bipolar derivations.

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Figure captions

Figure 1. The experimental setup. (A) The participant's index finger was taped to the vertically moving pneumatic muscle, and an accelerometer was taped to the nail of the finger. (B) EEG signals were recorded with a 58-electrode cap. (C) Participants sat on a chair with their head in the MEG sensor array.

Figure 2. Coherence spectra between finger acceleration and EEG signals averaged across all participants (n = 12). Coherence peaked at the 3-Hz-movement frequency and its harmonics. Black solid lines indicate session 1 and grey lines session 2 averages. The number of participants showing significant coherence at 3 Hz are indicated above the 3-Hz peak for session 1 and session 2 separately.

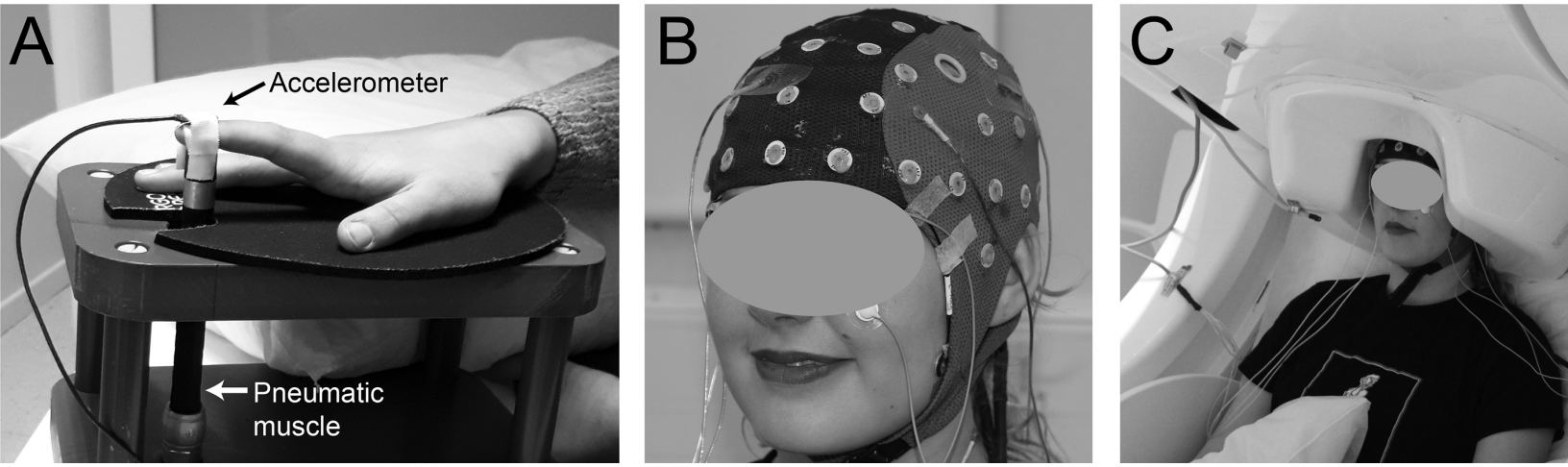
Figure 3. Mean CKC strength when the hands were pooled together for the three EEG derivations at session 1 and session 2. The error bars represent standard deviation. Horizontal bars indicate the significance of the difference between derivations.

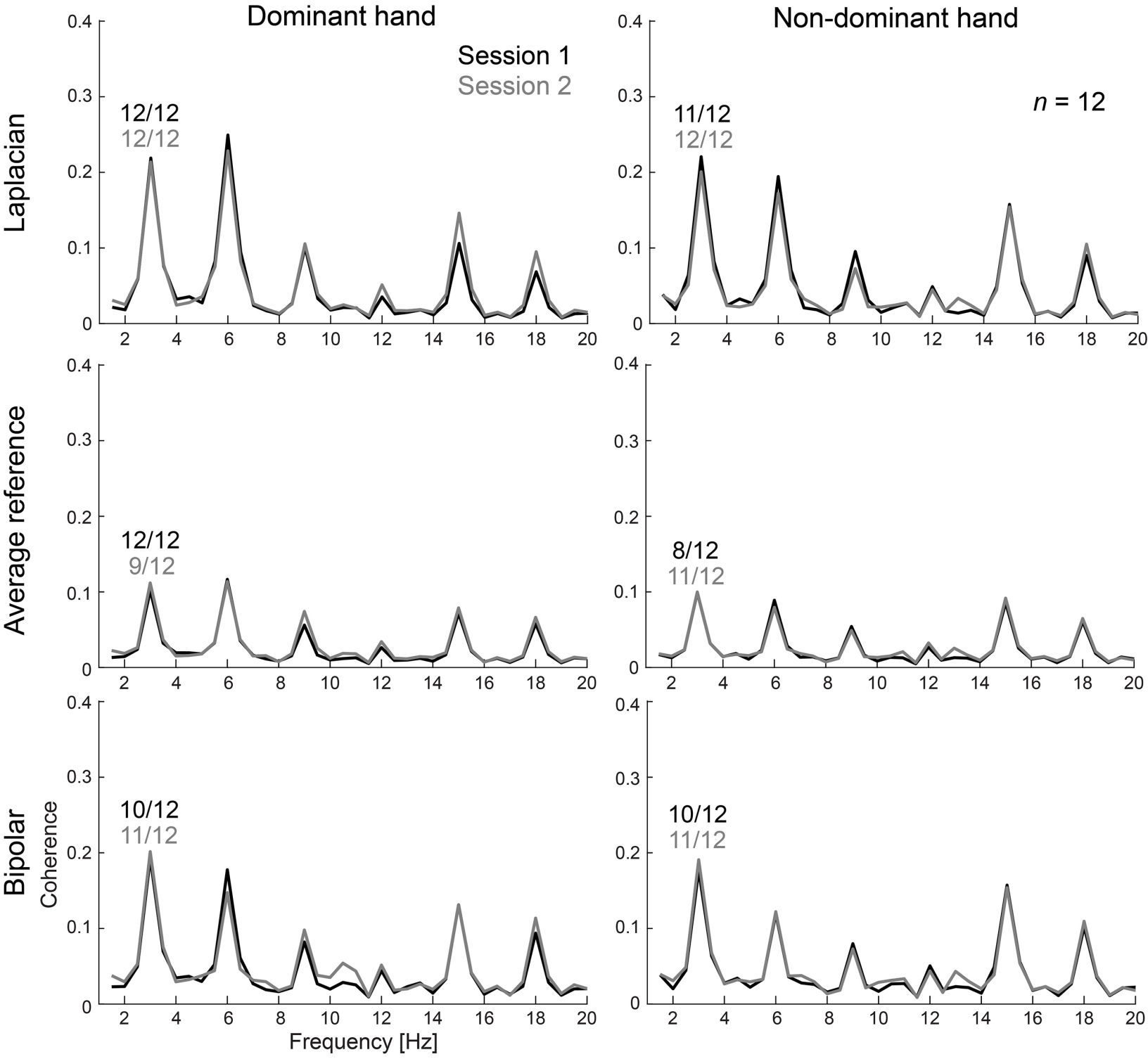
Figure 4. Inter-session and method correlations. A: Scatterplots for individual CKC values in session 1 and 2 for dominant and non-dominant hands separately. B: Scatterplots for individual CKC values pooled across the hands in session 1 for EEG (the three derivations) and MEG. Corresponding linear regression lines and Spearman correlation coefficients are given.

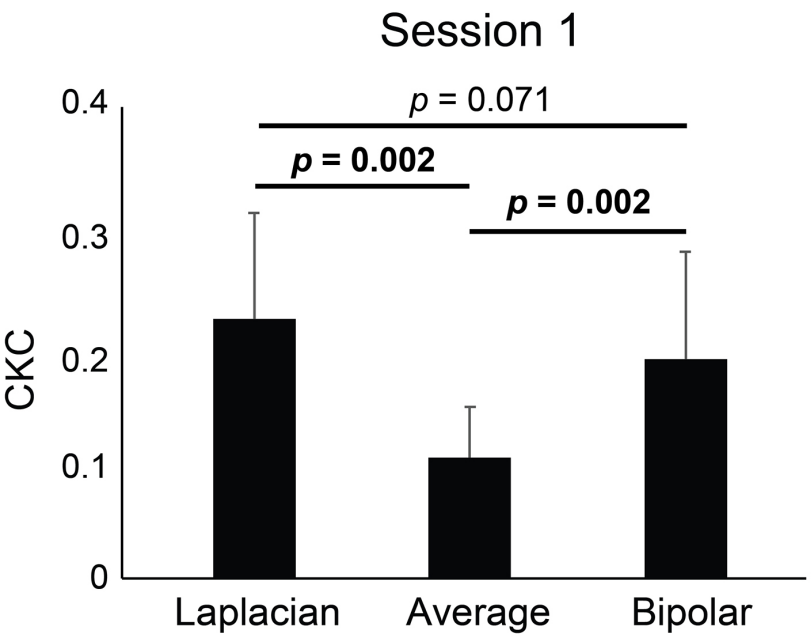
Figure 5. Topographic distributions of the mean CKC at 3 Hz across subjects (n = 12). There is one topography for each possible combination of derivation (surface Laplacian and average

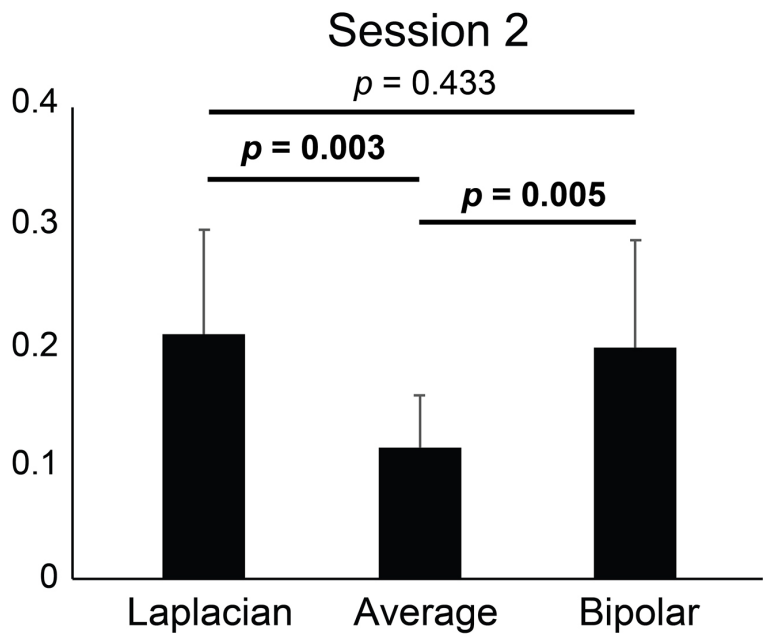
535 reference), moved finger and session. The overlaid numbers indicate the count of participants
536 showing peak CKC in each EEG electrode.

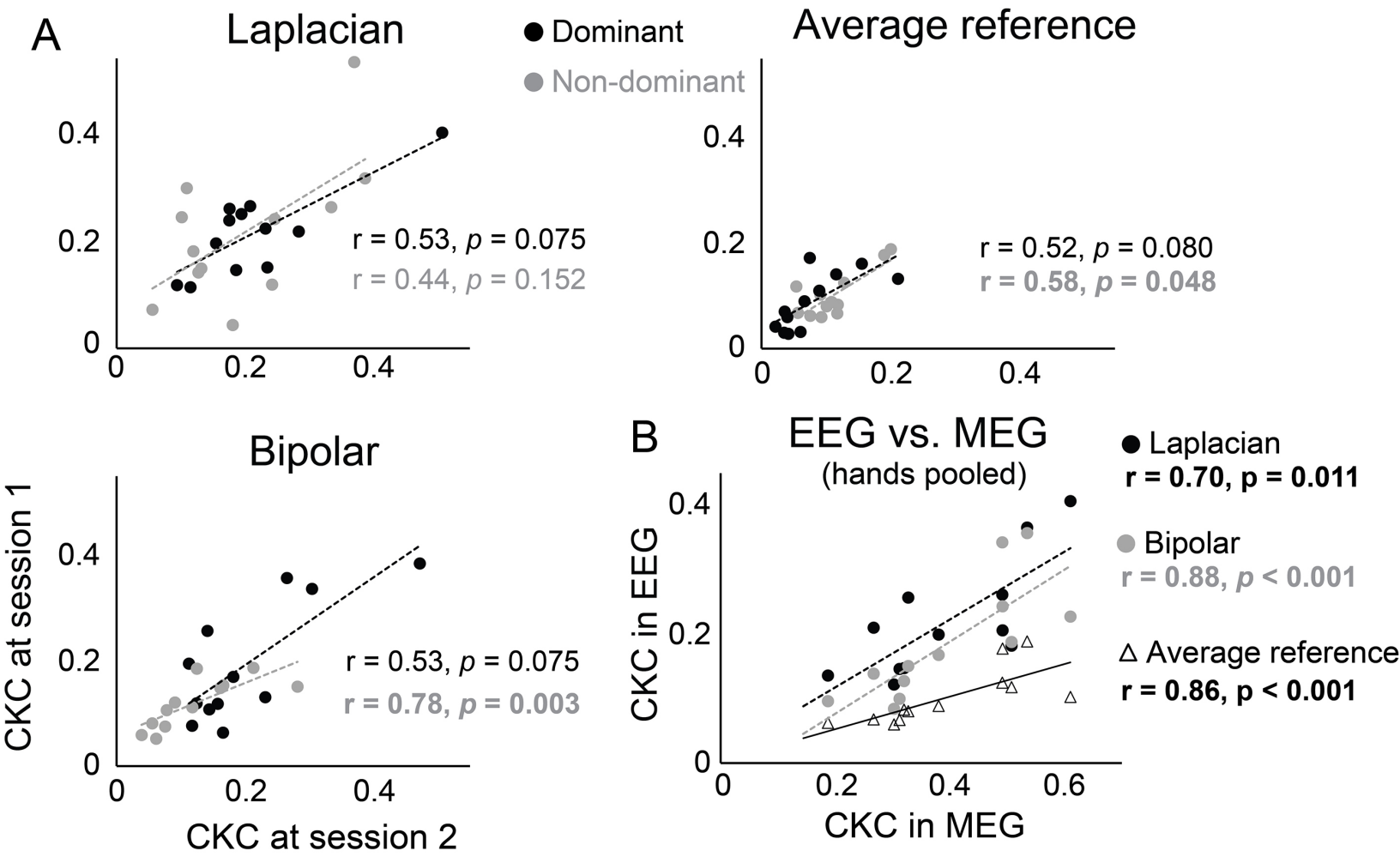
537 **Figure 6.** Bipolar EEG-electrode pairs with peak CKC value among all 1653 combinations. Line
538 thickness and darkness reflects occurrence (out of n = 12 x 2 sessions) of peak CKC in the given
539 electrode pair among the participants across both sessions. The narrowest and lightest line
540 indicates that there was only one occurrence of the peak CKC value.

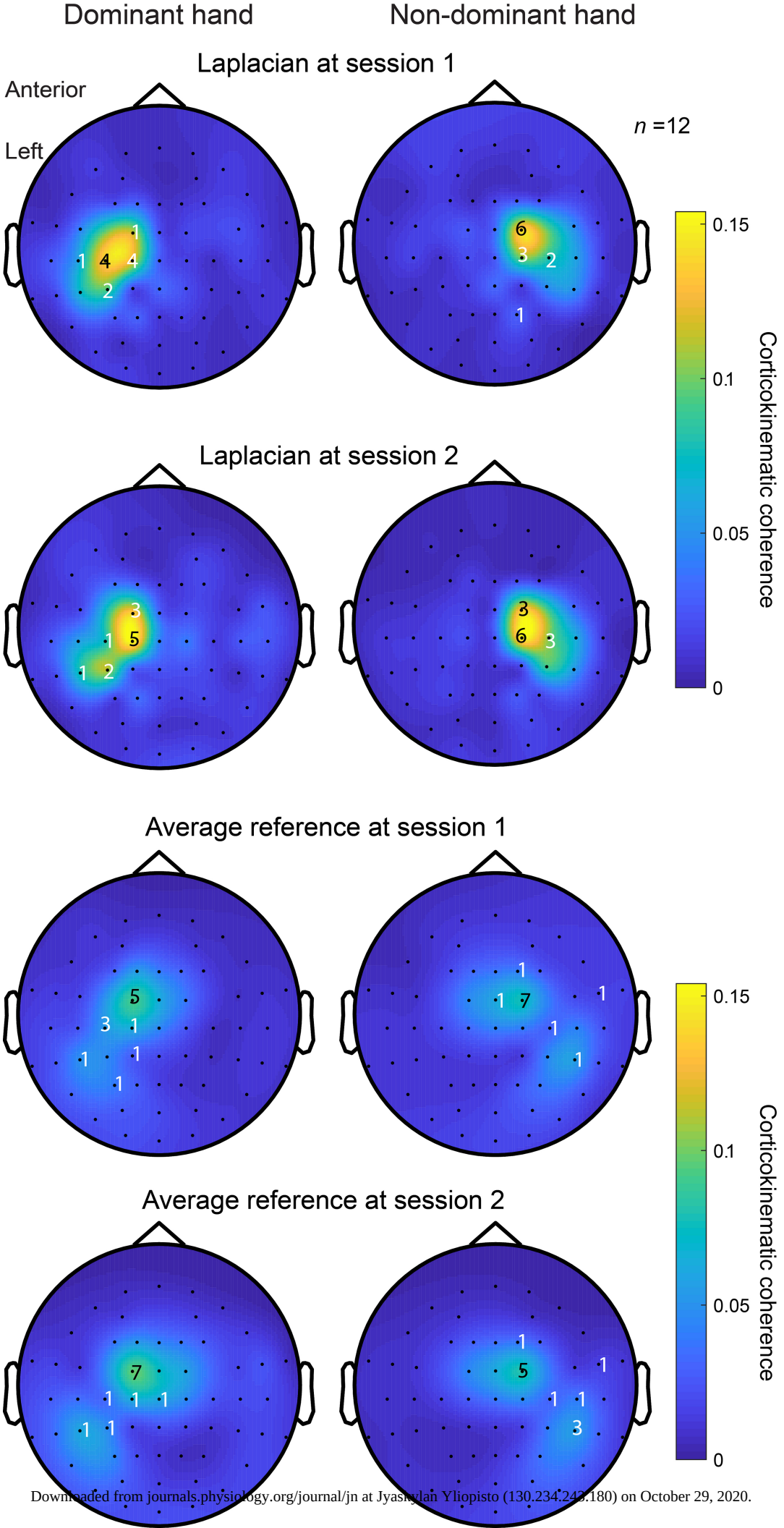












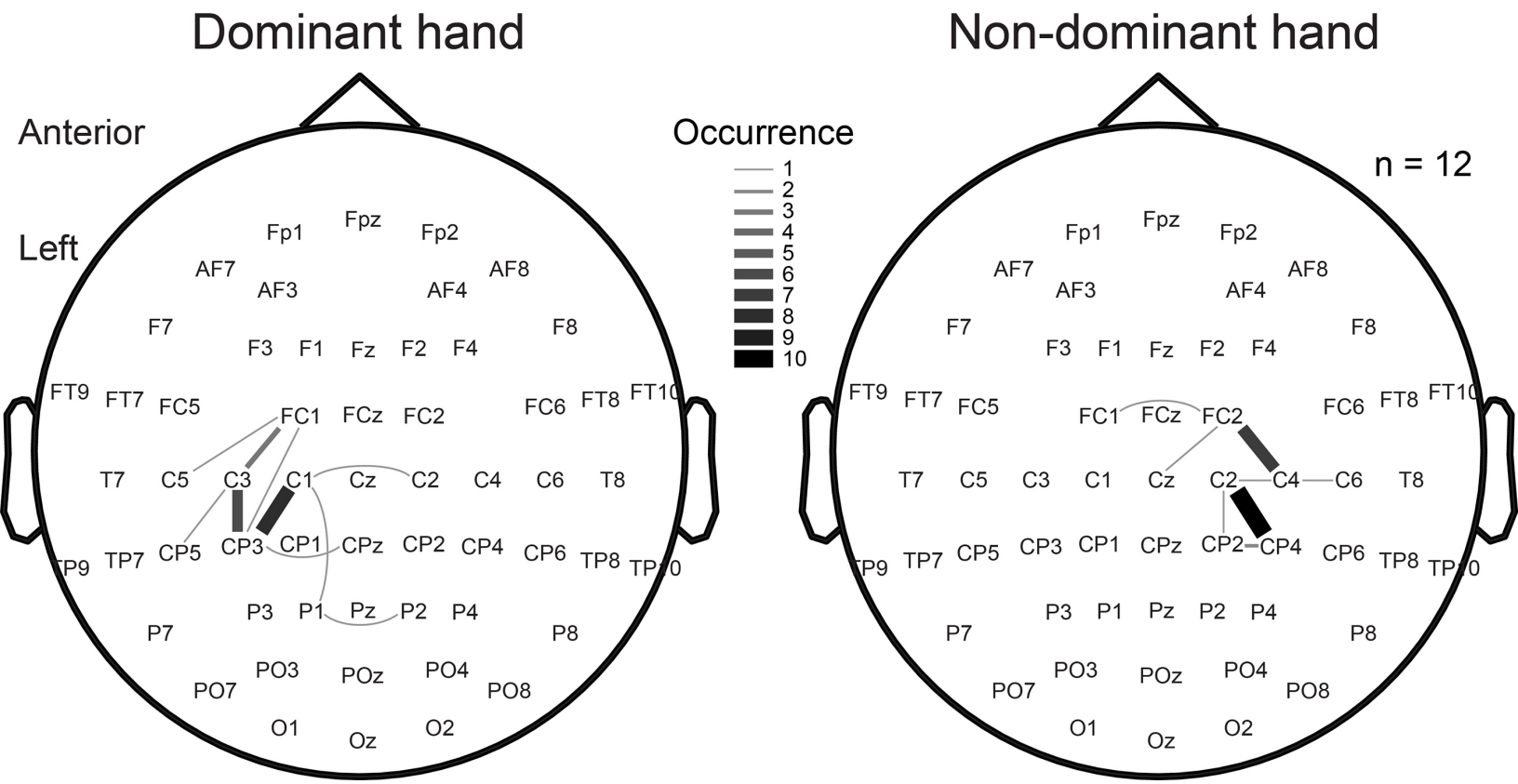


Table 1. CKC strength and number of subjects showing significant CKC (n-sig)

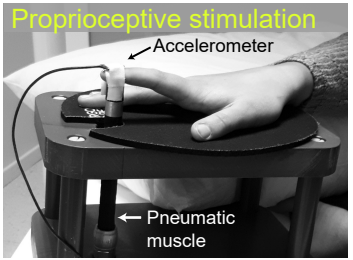
	Dominant			**Non-Dominant**		
	Session 1					
Approach	**Mean ± SD**	**Range**	**#(p<0.05)**	**Mean ± SD**	**Range**	**n-sig**
Laplacian	0.22 ± 0.08	0.12–0.41	12	0.22 ± 0.13	0.04–0.58	11
Average reference	0.10 ± 0.04	0.06–0.19	12	0.10 ± 0.06	0.03–0.24	8
Bipolar	0.19 ± 0.11	0.06–0.38	10	0.18 ± 0.09	0.06–0.33	10
	Session 2					
Laplacian	0.21 ± 0.11	0.09–0.51	12	0.20 ± 0.11	0.06–0.39	12
Average reference	0.11 ± 0.05	0.05–0.20	9	0.10 ± 0.05	0.02–0.19	11
Bipolar	0.20 ± 0.10	0.11–0.47	11	0.19 ± 0.11	0.06–0.36	11

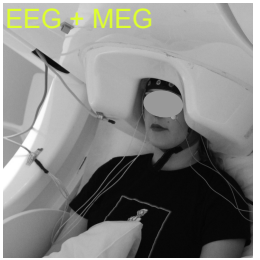
= number of subjects (out of 12) that reached statistical significance in level of $p < 0.05$ in CKC.

Table 2. Inter-session reproducibility of CKC.

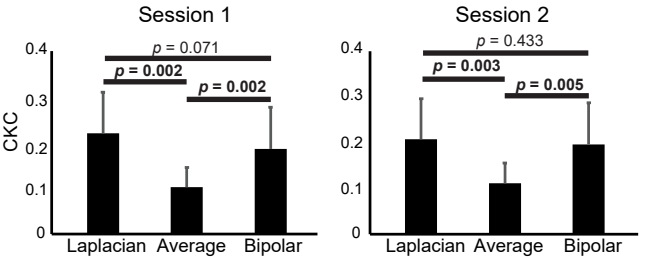
	Dominant		Non-Dominant	
Approach	**ICC**	**Spearman r**	**ICC**	**Spearman r**
Laplacian	0.88	0.53	0.76	0.44
Average reference	0.88	0.52	0.74	0.58*
Bipolar	0.87	0.53	0.93	0.78**

* = $p < 0.05$, ** = $p < 0.01$ for Spearman correlation coefficient.

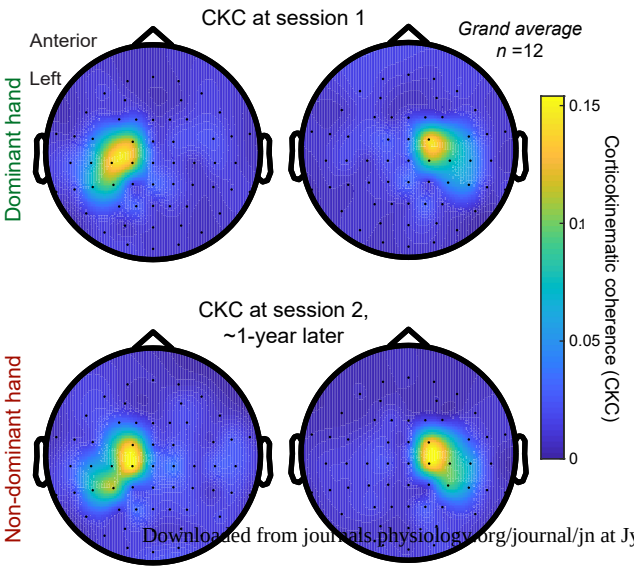




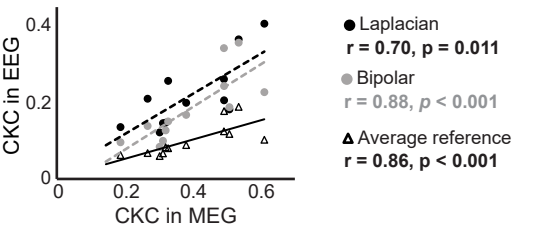
CKC strength for different EEG derivations



Corticokinematic coherence (CKC) for EEG (Laplacian derivation)



CKC in EEG vs. MEG (hands pooled together)



Bipolar electrode pairs showing peak CKC